Formal Genetics of Humans:
Modes of Inheritance

Dr. S Hosseini-Asl

Autosomal dominant (AD)

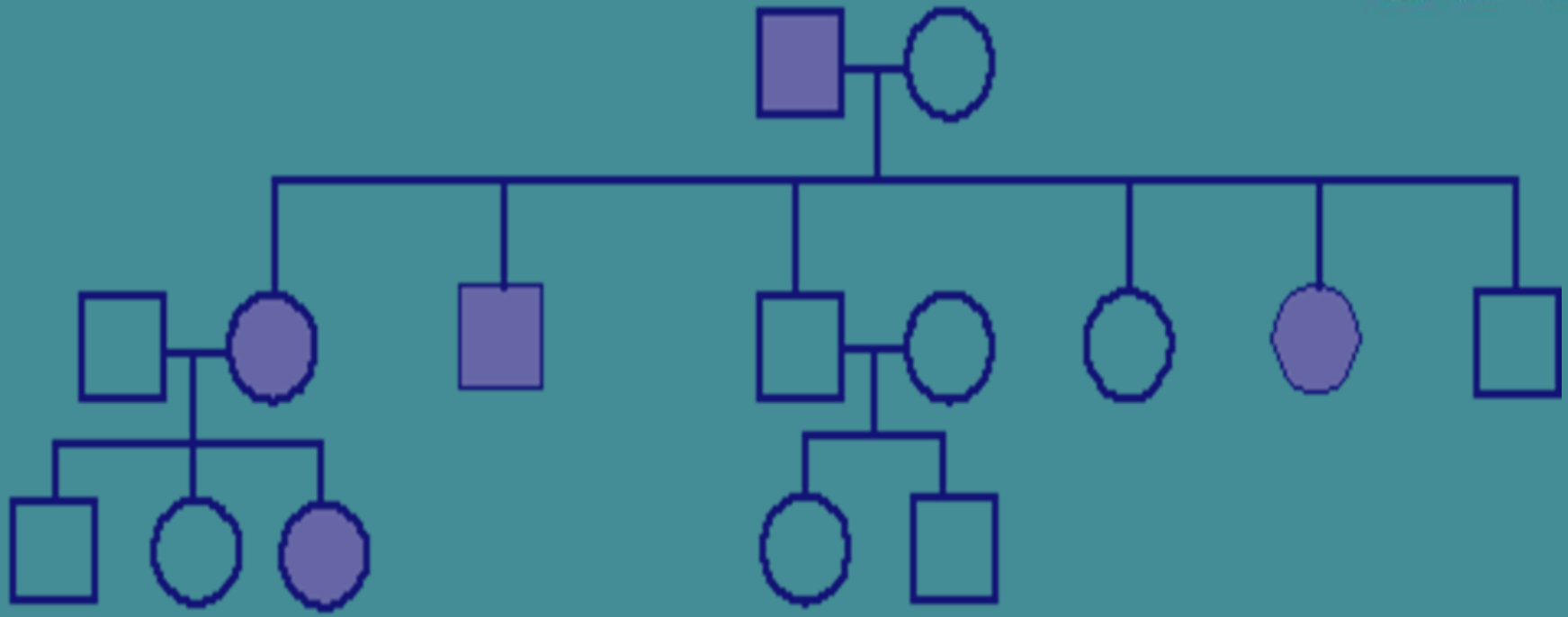
- a: Wild type (Wt) allele
- A: Mutant allele

- aa: Normal phenotype
- Aa: Affected (heterozygous)
- AA: Affected (homozygous)

- Frequency:

  f(aa) > f(AA) + f(Aa)

  f(Aa) > f(AA)



Inheritance of an Autosomal Dominant Trait
(Example: Huntington's Disease)

Autosomal dominant

AA × AA → AA (all)

AA × Aa → AA : Aa

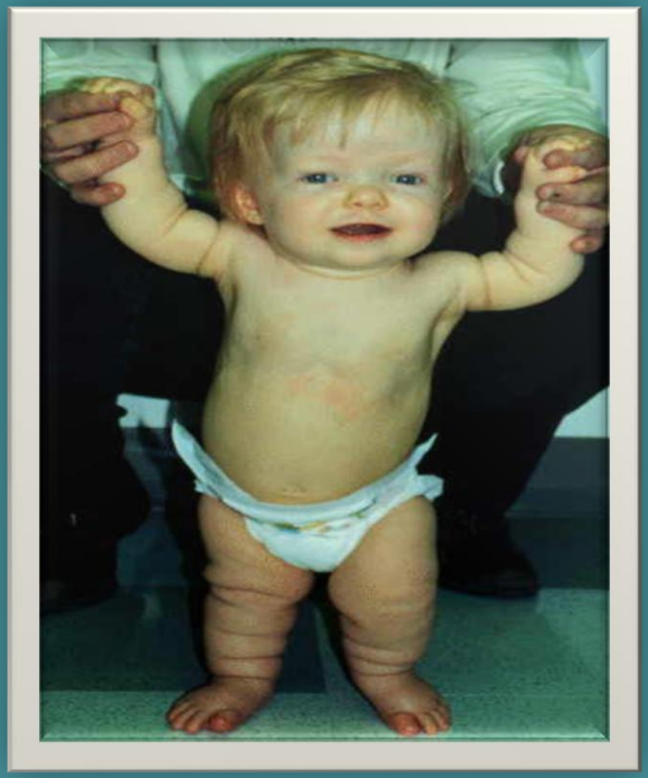
Aa × Aa → AA : Aa : Aa : aa

AA ← (AA × AA) or (AA × Aa) or (Aa × Aa)

Aa ← (AA × Aa) or (Aa × Aa) or (AA × aa) or (Aa × aa)

Achondroplasia

- A skeletal disorder of short-limbed dwarfism and large head size.



Achondroplasia

272

273

274

275

276

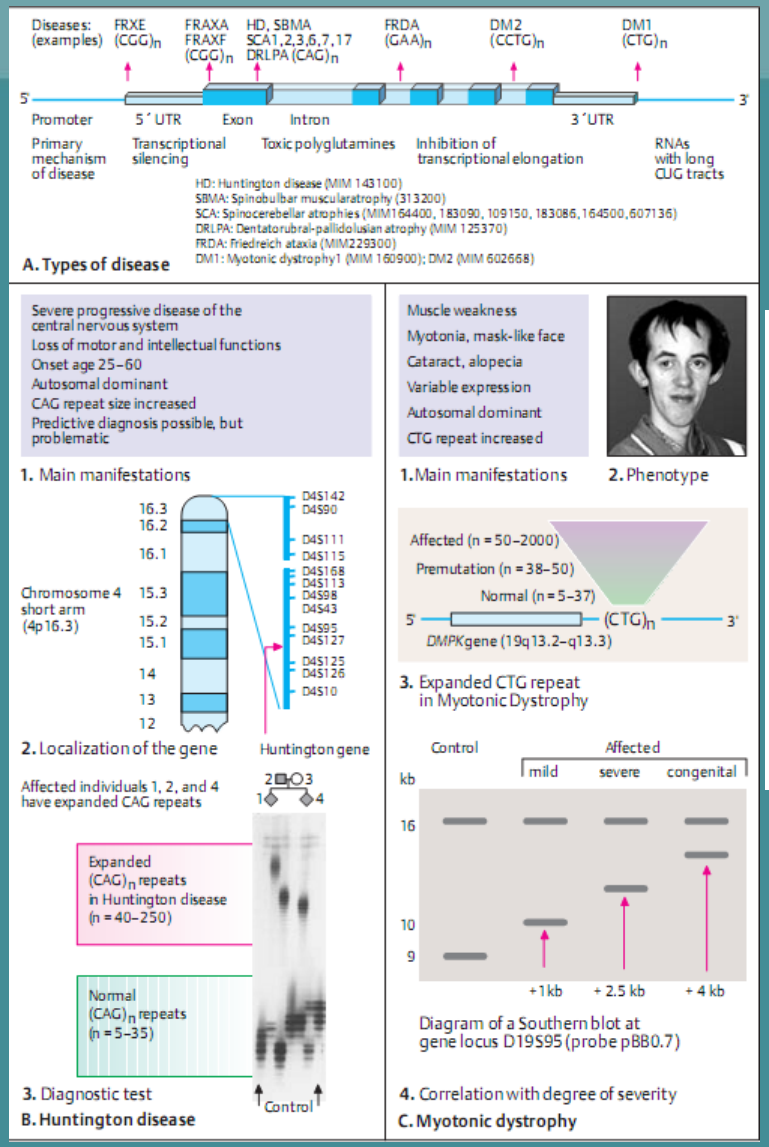
272–276 Achondroplasia.
Note: Photo – short stature, large head, prominent forehead, mid-face hypoplasia, genu varum, 'trident' hands and lumbar lordosis.
X-rays: Decreasing interpeduncular distance from thoracic to lumbar spine, short round iliac crests, narrow sacro-sciatic notches, horizontal acetabular roof and oval translucency of proximal femora.
Inheritance: Autosomal dominant, about 70–80% of cases are new mutations.

Huntington disease (HD)

- A neurodegenerative disease characterized by progressive dimentia and abnormal movements.

- (Same clinical expression in both homozygotes and heterozygotes)

Huntington disease (HD)



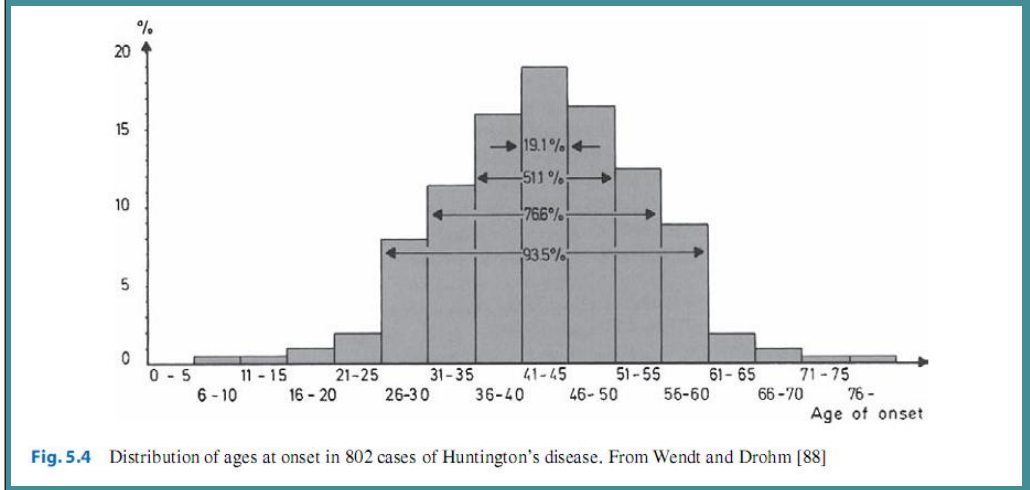


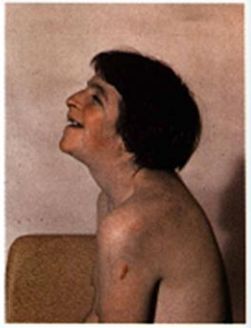
Fig. 5.4 Distribution of ages at onset in 802 cases of Huntington's disease. From Wendt and Drohm [88]

Some Disorders with AD inheritance

77

78

79



80

81

82

81 and 82 Freeman–Sheldon syndrome.
Note: Full forehead, blepharophimosis, hypoplastic alae, long philtrum, small mouth with puckered lips, H-shaped depression below lower lip. Ulnar deviated fingers with contractures ('Windmill vane'), talipes equinovarus with contractures of toes and vertical talus.
Other features: Kyphoscoliosis.
Inheritance: Mostly autosomal dominant. Occasional autosomal recessive pedigrees described.

100 and 101 Ectrodactyly, ectodermal dysplasia and clefting (EEC) syndrome.
Note: Repaired cleft lip, sparse, dry hair and split hand with partial syndactyly.
Other features: Small or missing teeth.
Inheritance: Autosomal dominant.

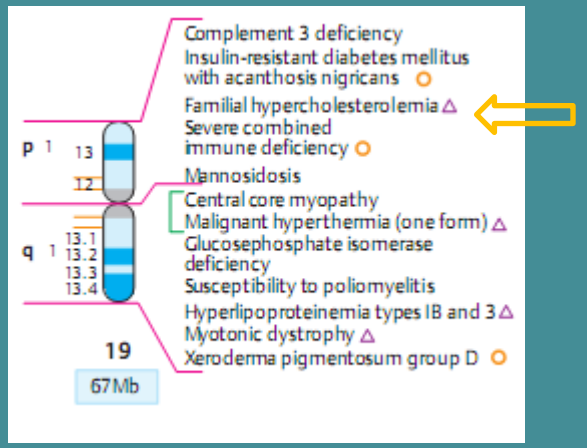
100

101

Familial Hypercholesterolemia (FH)

- Premature coronary hearth disease

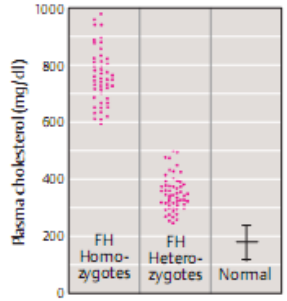
- Mutation in LDL receptor gene



FH

- Low-density lipoprotein (LDL) and cholesterol elevated in blood plasma
- Premature arteriosclerosis
- Xanthoma in skin and tendons
- Decreased life expectancy
- Autosomal dominant
- Mutation in LDL receptor gene

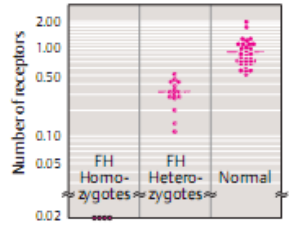
1. General features



2. Hypercholesterolemia

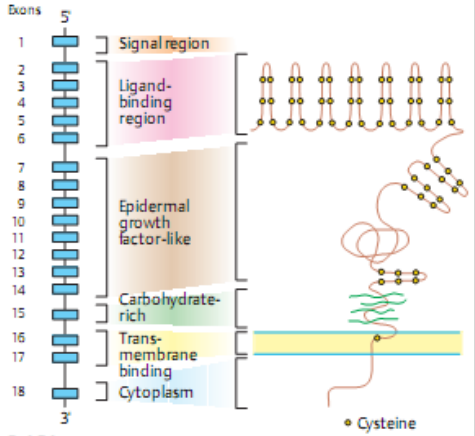
3. Arcus lipoides

4. Xanthoma formation

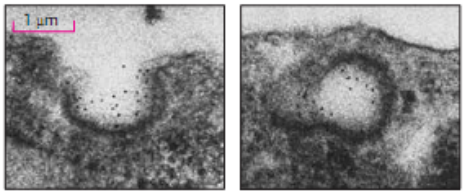


5. LDL receptors decreased

A. Familial hypercholesterolemia



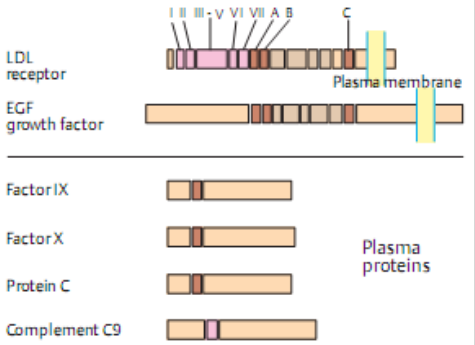
B. LDL receptor



1. Coated pit 2. Endocytotic vesicle

Electron micrographs of fibroblasts in culture that have taken up LDL molecules (black dots, made visible by binding to ferritin).

C. Receptor-mediated endocytosis of LDL



D. Homology with other proteins

Autosomal recessive (AR)

- A: Wt
- a: M

- AA: Normal phenotype
- Aa: Normal (carrier)
- aa: Affected

- Frequency:

f(aa) < f(AA) + f(Aa)

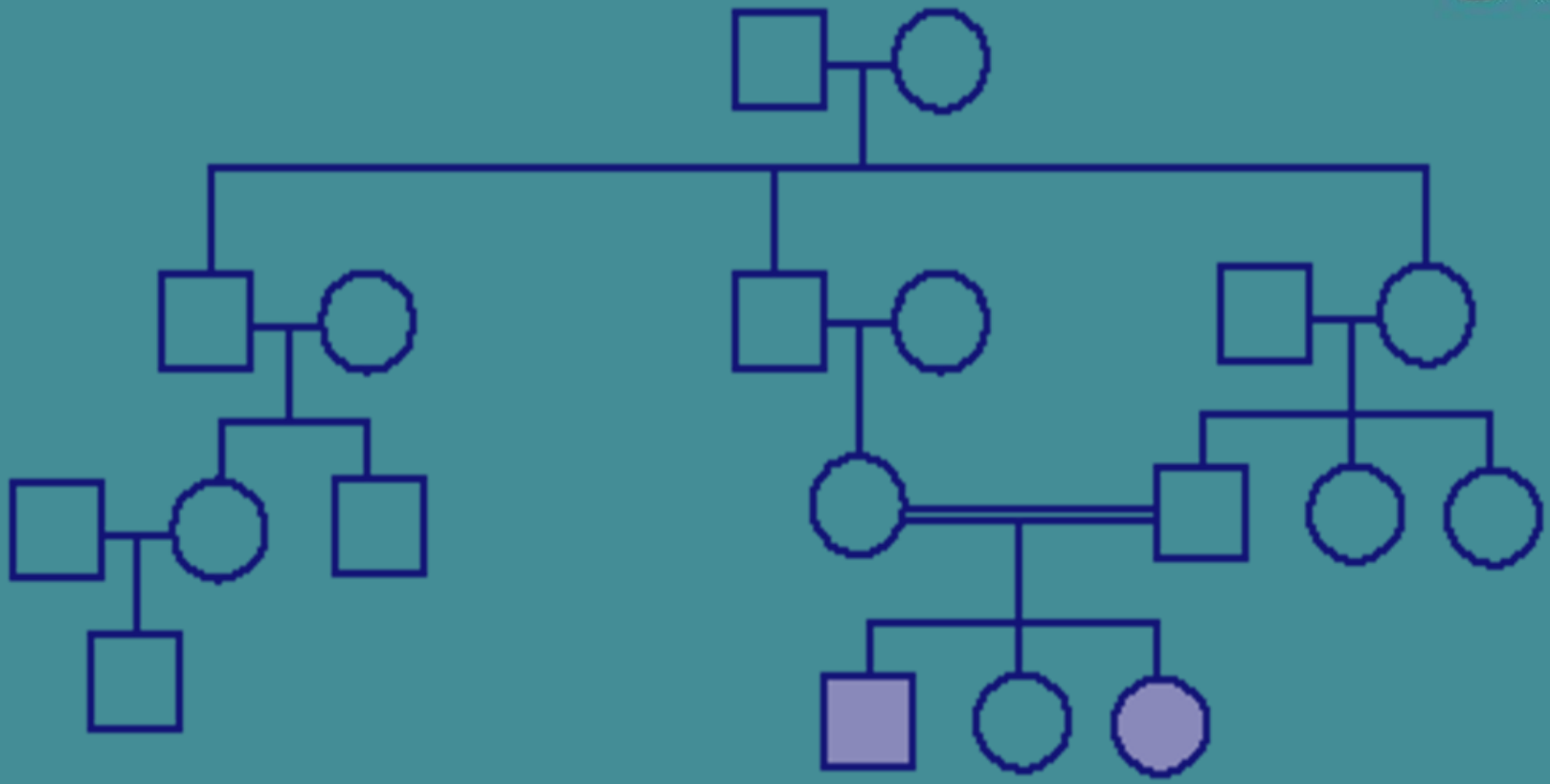
f(Aa) < f(AA)

Autosomal recessive

Aa × Aa → AA : Aa : Aa : aa

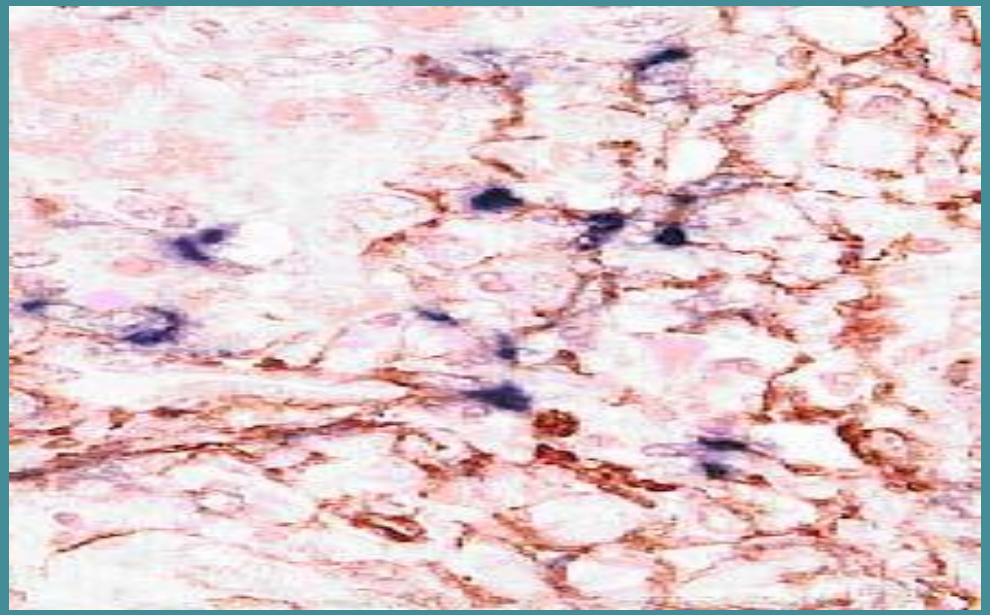
aa × aa → aa (all)

Aa × aa → Aa : aa



Inheritance of an Autosomal Recessive Trait

Cystic Fibrosis (CF)

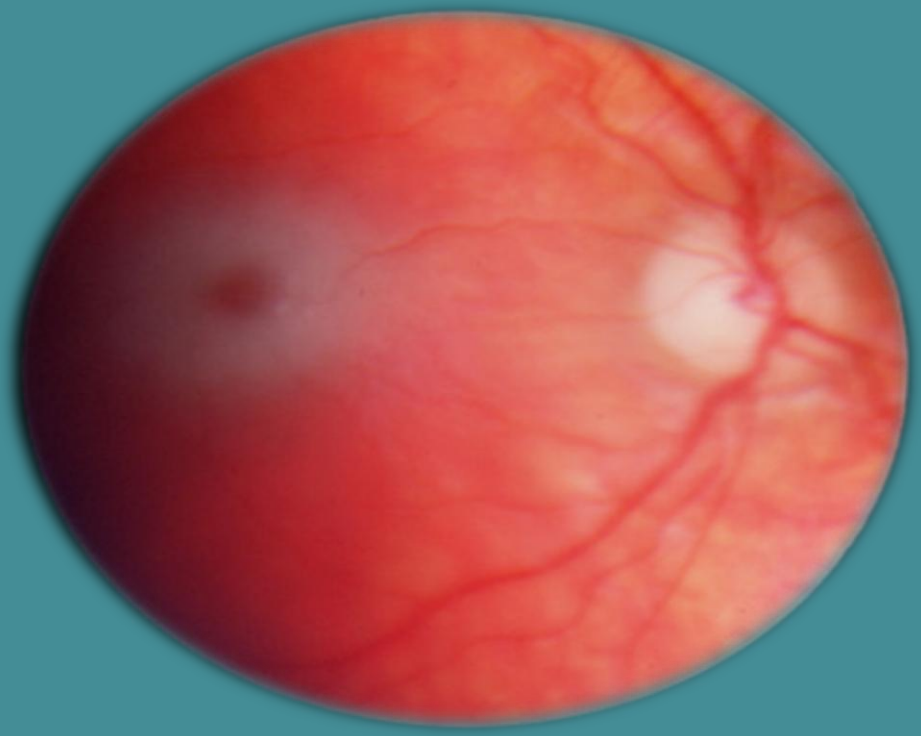


566

566 Cystic fibrosis.
Note: Emaciated appearance in a neonate, distended abdomen.
Other features: Meconium ileus, steatorrhoea, chronic pulmonary disease, salt loss and dehydration.
Inheritance: Autosomal recessive.

Tay-Sachs disease (GM2-Gangliosidosis)

Affected infants appear normal until about 3-6 months of age but then gradually undergo progressive neurological deterioration until death at 2-4 years. The effects of neuronal cell death can be seen directly in the form of so-called cherry-red spot in the retina.



597

598

597 and 598 Sickle cell anaemia.
Note: Hypochromic anaemia with sickle and target cells.

X-ray: Note – 'hair on end' appearance of the bones of the cranial vault.

Inheritance: Autosomal recessive. Heterozygotes are very common in some parts of Africa and in peoples of African origin. Heterozygote detection is simple and should be carried out when couples of African origin marry. Antenatal diagnosis is possible both by fetal blood sampling and by DNA analysis of amniotic fluid cells. The disease is caused by a single amino-acid substitution in the ß-globin chain.

599 α-Thalassaemia.
Note: Hydrops fetalis in the severe lethal form.

Other features and inheritance: There are two ∝-globin loci. Clinical features depend on the number of ∝-globin genes absent (see **Table 24**). Antenatal diagnosis possible.

599

Table 24 Types of α-thalassaemia

Condition	Number of Hb α genes active	Clinical features	Main haemoglobins
Normal	4	—	A, A_2
'Silent carrier'	3	—	A, A_2
∝-Thal trait	2	Mild anaemia	A, A_2
Hb H disease	1	Severe anaemia	H($ß_4$) A
Hydrops fetalis	0	Hydrops, fetal demise	Barts (γ_4)

600

601

600 and 601 ß-Thalassaemia.
Note: Enlarged liver and spleen due to extramedullary haematopoiesis. The face on the right shows broadening of nasal bridge and alveolar ridge.

Other features: Anaemia, haemosiderosis and demise in the second decade.

Inheritance: Autosomal recessive, there are different molecular forms. Antenatal diagnosis possible by fetal blood sampling and DNA analysis of amniotic fluid cells in some cases.

Pseudodominance in Autosomal Recessive Inheritance

Occasionally matings between an unaffected heterozygote and an affected homozygote are observed. One parent is affected, and the expected segregation ratio among children is 1:1. Since this segregation pattern mimics that found with dominant inheritance, this situation is aptly named “pseudodominance.” Fortunately for genetic analysis, such matings are

very rare.

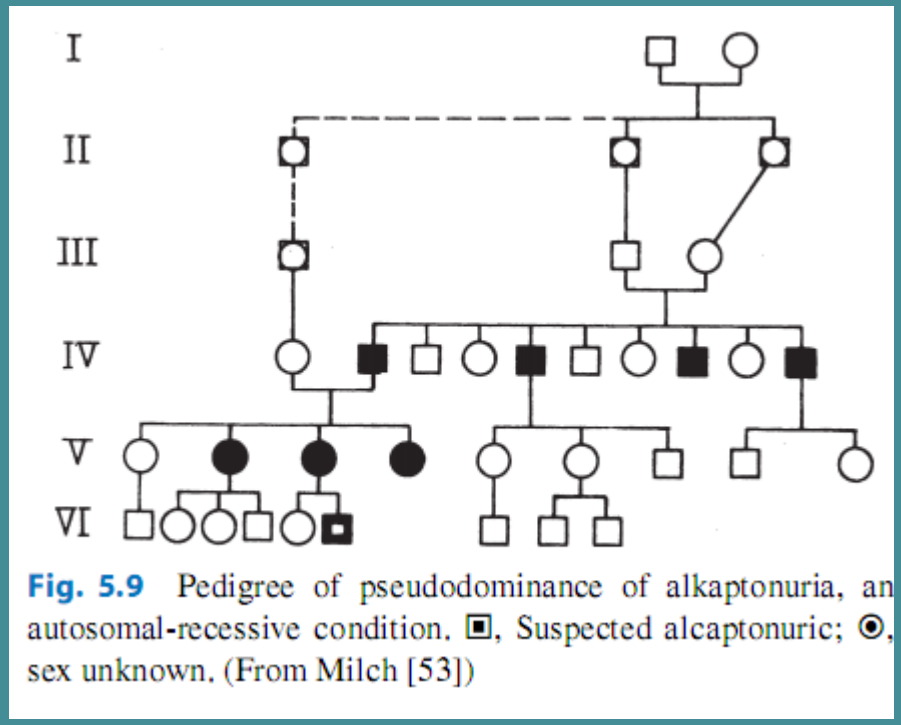


Fig. 5.9 Pedigree of pseudodominance of alkaptonuria, an autosomal-recessive condition. ▣, Suspected alcaptonuric; ⊙, sex unknown. (From Milch [53])

Genetic heterogeneity

(Harris, 1953; Fraser,1956)

An apparently uniform phenotype being caused by two or more different genotypes.

Allelic

Locus (Non-allelic)

A particular phenotype may be caused by mutations at different loci (locus heterogeneity) or by different mutant alleles at the same locus (allele heterogeneity).

Allelic heterogeneity

- Allelic heterogeneity is the phenomenon in which different mutations at the same locus causes a similar phenotype. For example, β-thalassemia may be caused by several different mutations in the β-globin gene.

- Wt: ----------A----------C----------
- M1: ----------G----------C----------
- M2: ----------A----------T----------

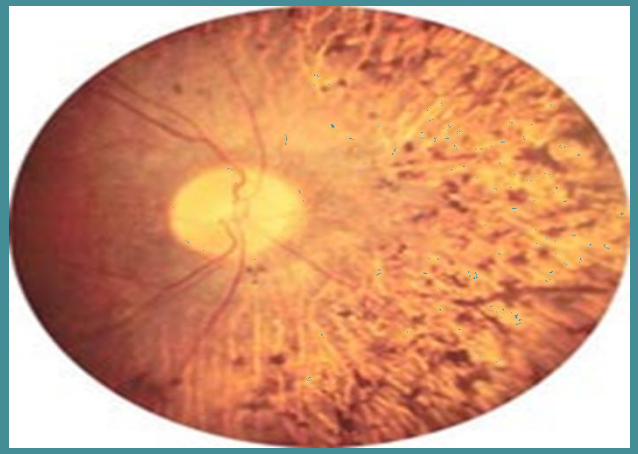
Locus heterogeneity

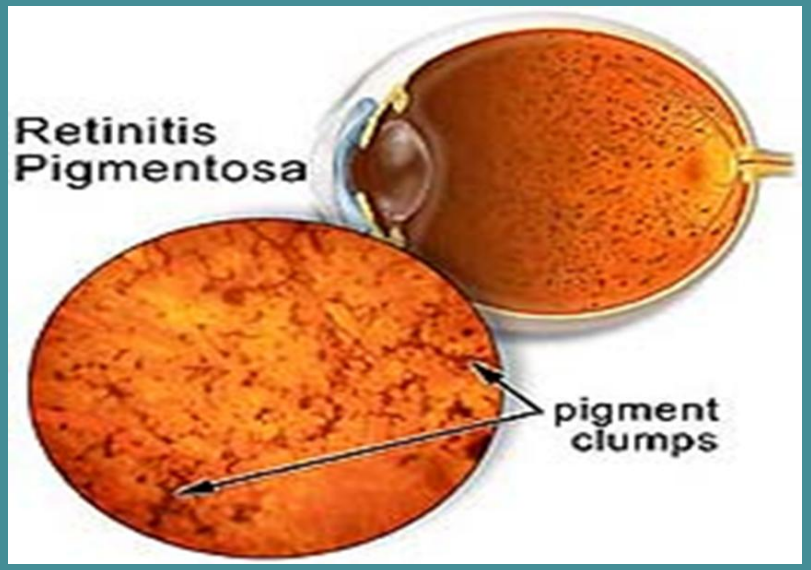
- Locus heterogeneity is a single disorder, trait, or pattern of traits caused by mutations in genes at different chromosomal loci.

Locus Heterogeneity

Retinitis Pigmentosa

- A common cause of visual impairment due to photoreceptor degeneration associated with abnormal pigment distribution in the retina.





A group of hereditary diseases with degeneration of photoreceptors in the retina

Night blindness

Progressive loss of vision

Frequency about 1:3500

Frequency of the different genetic forms

25% autosomal dominant
20% autosomal recessive
8% X-chromosomal
47% Mode of inheritance uncertain in an individual patient

Important diagnostic signs

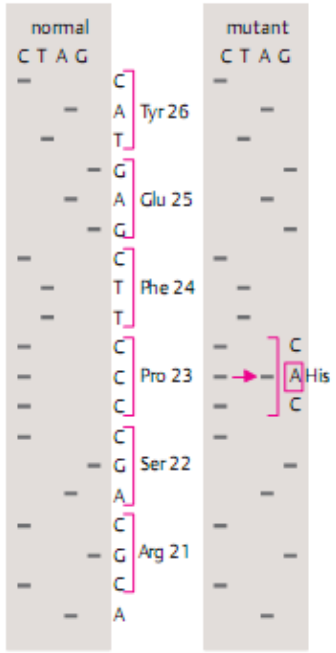
Fundus:
narrow vessels
pale optic nerve
macula changes
widened light reflex
pigment epithelium changes
electroretinogram extinguished

Secondary changes in the anterior chamber:
vitreous body changes

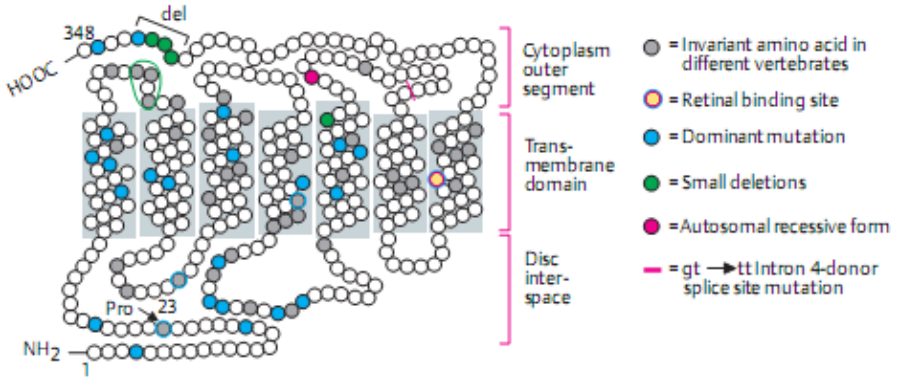
Cataract
Myopia

Typical fundus with pigment changes, narrow vessels, and pale, waxy optical nerve

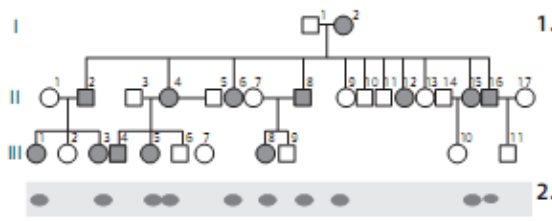
A. Retinitis pigmentosa



B. Mutation in rhodopsin



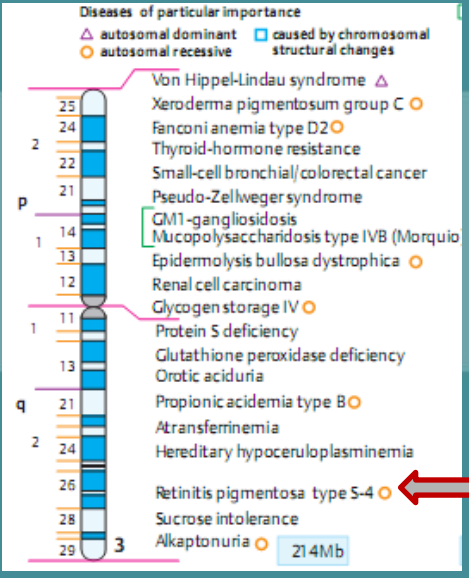
C. Mutations in rhodopsin

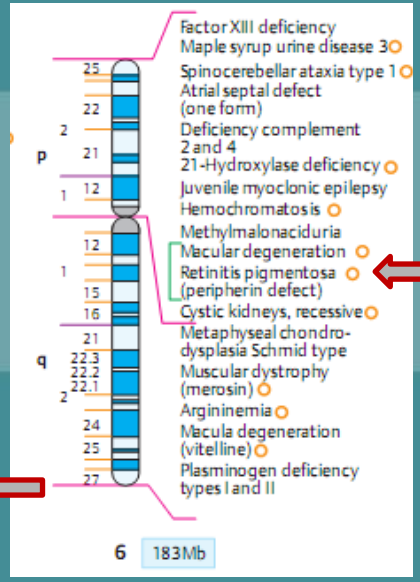


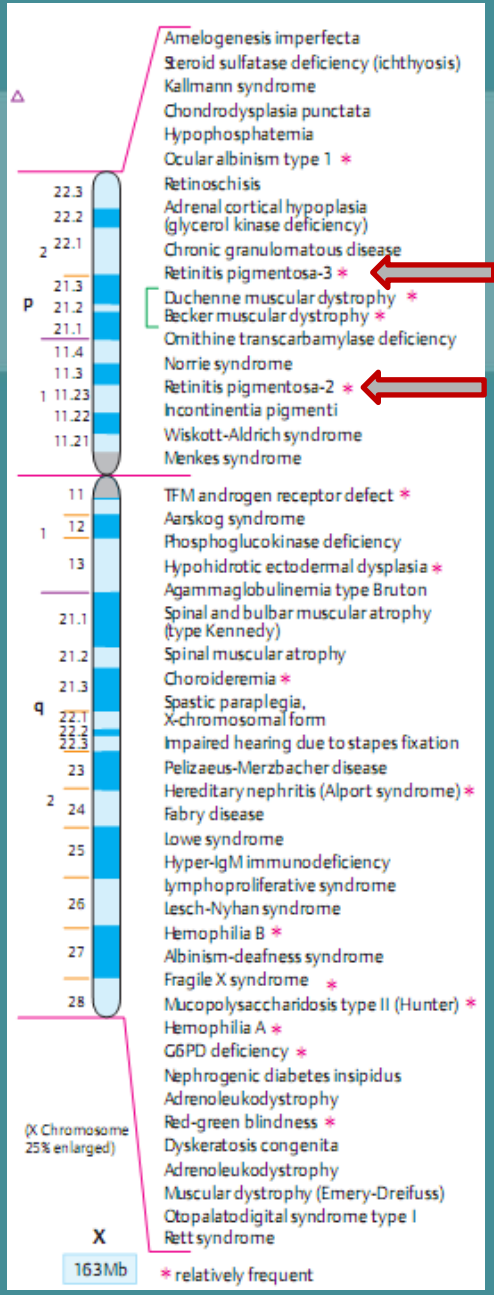
1. Pedigree with autosomal dominant retinitis pigmentosa due to mutation in codon 23 (P23H)

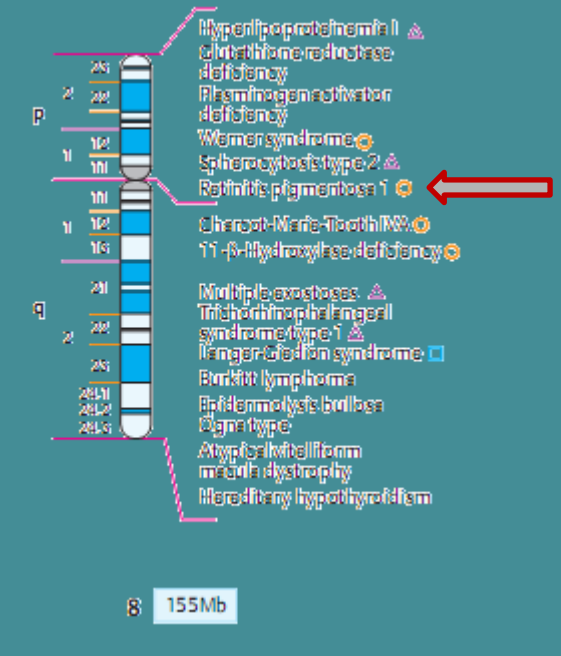
2. Autoradiogram of hybridization of amplified DNA fragments in codon 23 with oligomer 3'-CATGAGCTTCACCGACGCA-5' for the mutant sequence

D. Demonstration of mutation P23H in codon 23 by oligonucleotides after PCR


Diseases of particular importance
autosomal dominant
autosomal recessive
caused by chromosomal structural changes
Von Hippel-Lindau syndrome
Xeroderma pigmentosum group C
Fanconi anemia type D2
Thyroid-hormone resistance
Small-cell bronchial/colorectal cancer
Pseudo-Zellweger syndrome
GM1-gangliosidosis
Mucopolysaccharidosis type IVB (Morquio
Epidermolysis bullosa dystrophica
Renal cell carcinoma
Glycogen storage IV
Protein S deficiency
Glutathione peroxidase deficiency
Orotic aciduria
Propionic acidemia type B
Atransferrinemia
Hereditary hypoceruloplasminemia
Retinitis pigmentosa type S-4
Sucrose intolerance
Alkaptonuria
3
214Mb


Factor XIII deficiency
Maple syrup urine disease 3
Spinocerebellar ataxia type 1
Atrial septal defect (one form)
Deficiency complement 2 and 4
21-Hydroxylase deficiency
Juvenile myoclonic epilepsy
Hemochromatosis
Methylmalonaciduria
Macular degeneration
Retinitis pigmentosa (peripherin defect)
Cystic kidneys, recessive
Metaphyseal chondro-dysplasia Schmid type
Muscular dystrophy (merosin)
Argininemia
Macula degeneration (vitelline)
Plasminogen deficiency types I and II
6
183Mb


Amelogenesis imperfecta
Steroid sulfatase deficiency (ichthyosis)
Kallmann syndrome
Chondrodysplasia punctata
Hypophosphatemia
Ocular albinism type 1
Retinoschisis
Adrenal cortical hypoplasia (glycerol kinase deficiency)
Chronic granulomatous disease
Retinitis pigmentosa-3
Duchenne muscular dystrophy
Becker muscular dystrophy
Ornithine transcarbamylase deficiency
Norrie syndrome
Retinitis pigmentosa-2
Incontinentia pigmenti
Wiskott-Aldrich syndrome
Menkes syndrome
TFM androgen receptor defect
Aarskog syndrome
Phosphoglucokinase deficiency
Hypohidrotic ectodermal dysplasia
Agammaglobulinemia type Bruton
Spinal and bulbar muscular atrophy (type Kennedy)
Spinal muscular atrophy
Choroideremia
Spastic paraplegia, X-chromosomal form
Impaired hearing due to stapes fixation
Pelizaeus-Merzbacher disease
Hereditary nephritis (Alport syndrome)
Fabry disease
Lowe syndrome
Hyper-IgM immunodeficiency lymphoproliferative syndrome
Lesch-Nyhan syndrome
Hemophilia B
Albinism-deafness syndrome
Fragile X syndrome
Mucopolysaccharidosis type II (Hunter)
Hemophilia A
G6PD deficiency
Nephrogenic diabetes insipidus
Adrenoleukodystrophy
Red-green blindness
Dyskeratosis congenita
Adrenoleukodystrophy
Muscular dystrophy (Emery-Dreifuss)
Otopalatodigital syndrome type I
Rett syndrome
(X Chromosome 25% enlarged)
X
163Mb
relatively frequent


Hyperlipoproteinemia I
Glutathione reductase deficiency
Plasminogen activator deficiency
Werner syndrome
Spherocytosis type 2
Retinitis pigmentosa 1
Charcot-Marie-Tooth IV
11-β-Hydroxylase deficiency
Multiple exostoses
Trichorhinophalangeal syndrome type 1
Langer-Giedion syndrome
Burkitt lymphoma
Epidermolysis bullosa Ogna type
Atypical vitelliform macula dystrophy
Hereditary hypothyroidism
8
155Mb

Locus Heterogeneity

Ehlers-Danlos syndrome

I. **AD**

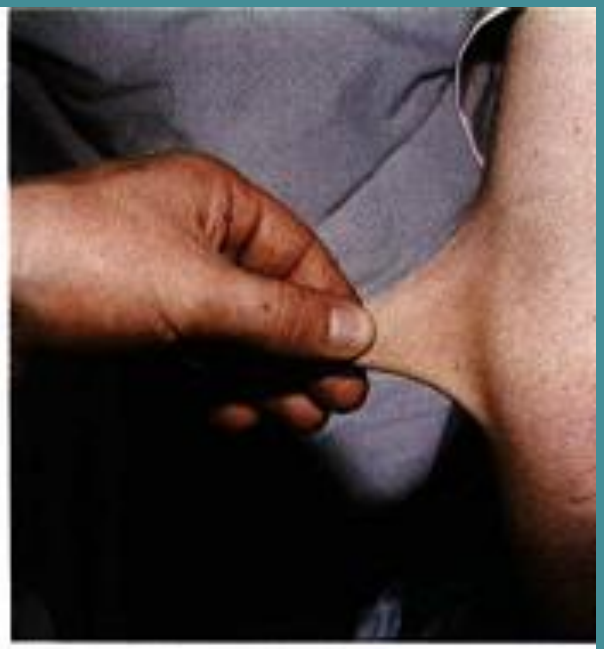
II. **A**

III. **X-linked**

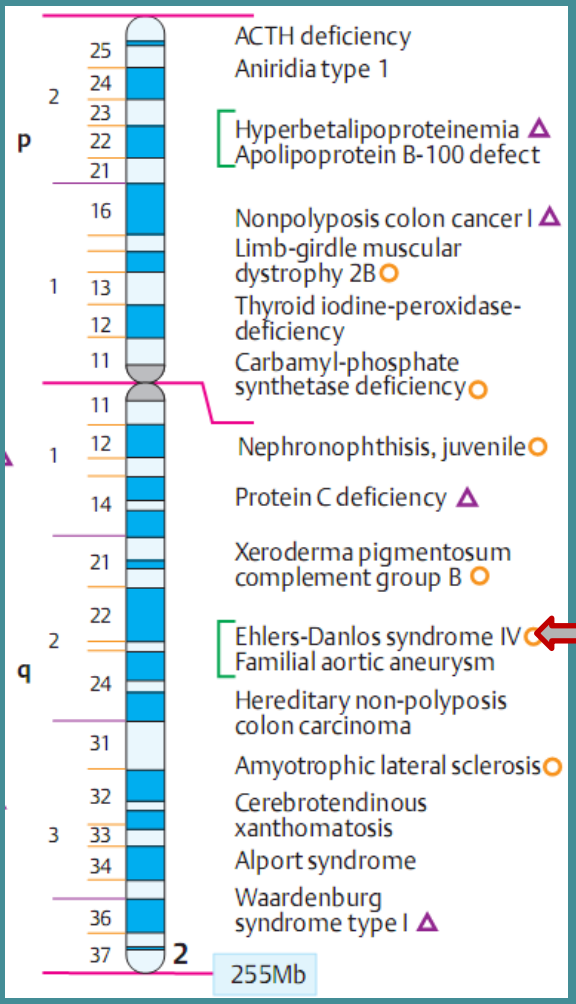
(more than 10 different loci)

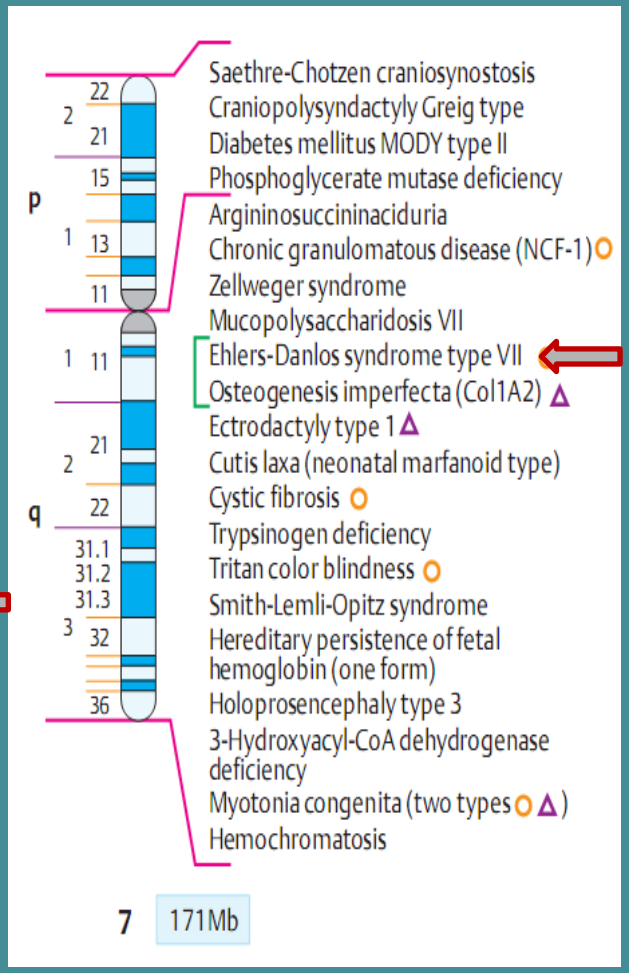
Ehlers-Danlos syndrome

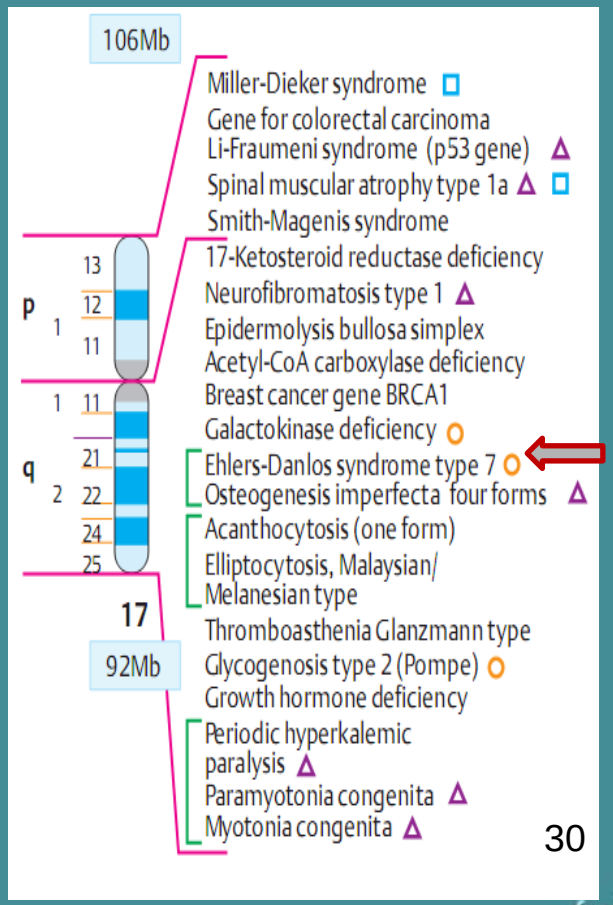
- Skin and other connective tissues may be exclusively elastic or fragile because of an underlying defect of collagen structure.



438 and 439 Ehlers–Danlos syndrome.
Note: Hyperextensible skin and joints.
Other features: See **Table 8**.
Inheritance: See **Table 8**.


ACTH deficiency
Aniridia type 1
Hyperbetalipoproteinemia
Apolipoprotein B-100 defect
Nonpolyposis colon cancer I
Limb-girdle muscular dystrophy 2B
Thyroid iodine-peroxidase-deficiency
Carbamyl-phosphate synthetase deficiency
Nephronophthisis, juvenile
Protein C deficiency
Xeroderma pigmentosum complement group B
Ehlers-Danlos syndrome IV
Familial aortic aneurysm
Hereditary non-polyposis colon carcinoma
Amyotrophic lateral sclerosis
Cerebrotendinous xanthomatosis
Alport syndrome
Waardenburg syndrome type I
2
255Mb


Saethre-Chotzen craniosynostosis
Craniopolysyndactyly Greig type
Diabetes mellitus MODY type II
Phosphoglycerate mutase deficiency
Argininosuccininaciduria
Chronic granulomatous disease (NCF-1)
Zellweger syndrome
Mucopolysaccharidosis VII
Ehlers-Danlos syndrome type VII
Osteogenesis imperfecta (Col1A2)
Ectrodactyly type 1
Cutis laxa (neonatal marfanoid type)
Cystic fibrosis
Trypsinogen deficiency
Tritan color blindness
Smith-Lemli-Opitz syndrome
Hereditary persistence of fetal hemoglobin (one form)
Holoprosencephaly type 3
3-Hydroxyacyl-CoA dehydrogenase deficiency
Myotonia congenita (two types)
Hemochromatosis
7
171Mb


106Mb
Miller-Dieker syndrome
Gene for colorectal carcinoma
Li-Fraumeni syndrome (p53 gene)
Spinal muscular atrophy type 1a
Smith-Magenis syndrome
17-Ketosteroid reductase deficiency
Neurofibromatosis type 1
Epidermolysis bullosa simplex
Acetyl-CoA carboxylase deficiency
Breast cancer gene BRCA1
Galactokinase deficiency
Ehlers-Danlos syndrome type 7
Osteogenesis imperfecta four forms
Acanthocytosis (one form)
Elliptocytosis, Malaysian/ Melanesian type
Thromboasthenia Glanzmann type
Glycogenosis type 2 (Pompe)
Growth hormone deficiency
Periodic hyperkalemic paralysis
Paramyotonia congenita
Myotonia congenita
17
92Mb

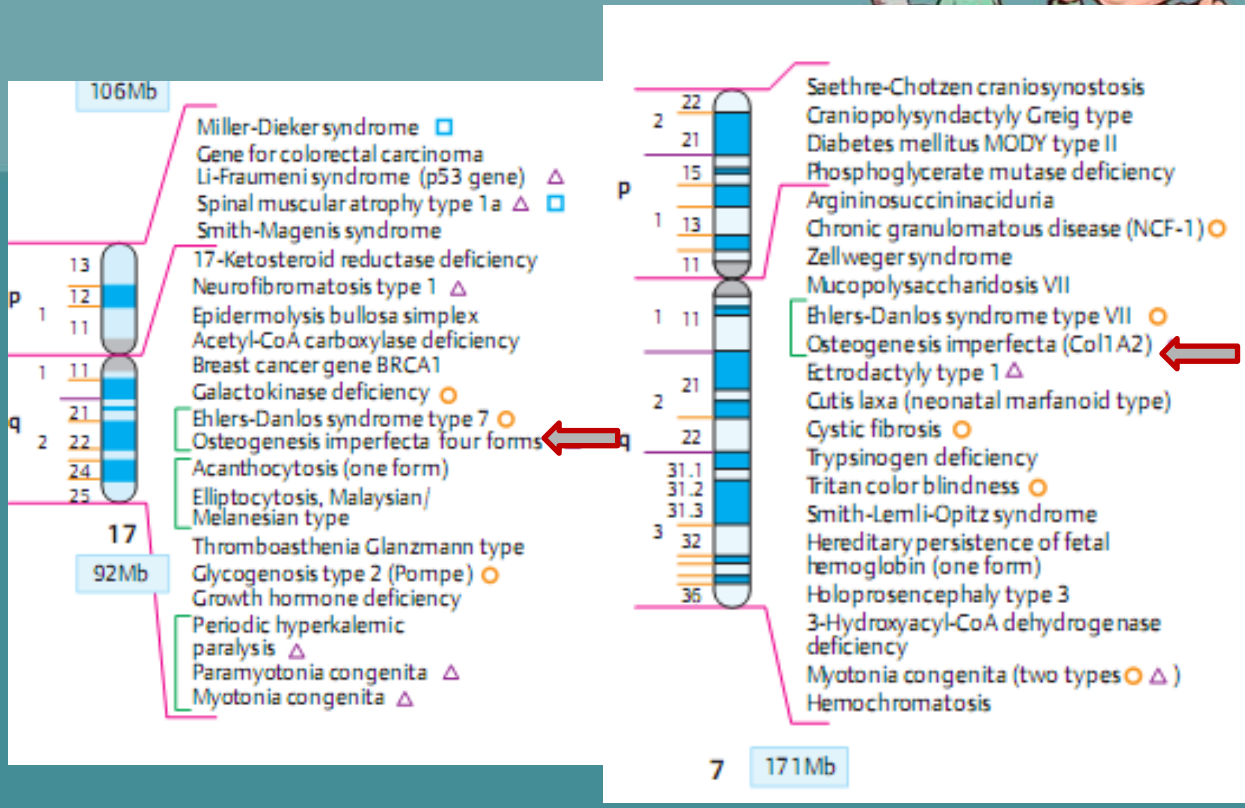
Locus Heterogeneity

Osteogenesis Imperfecta

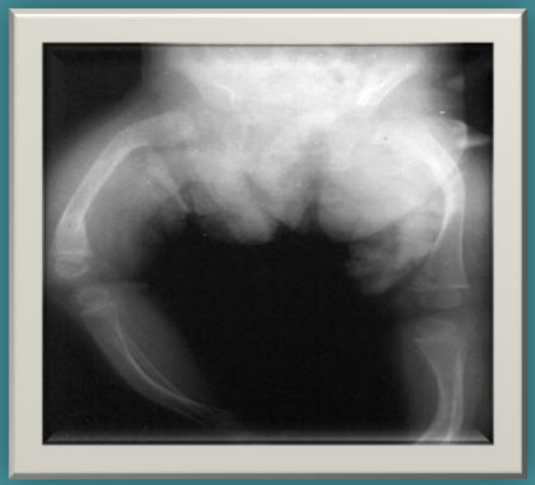
I. Chr.17

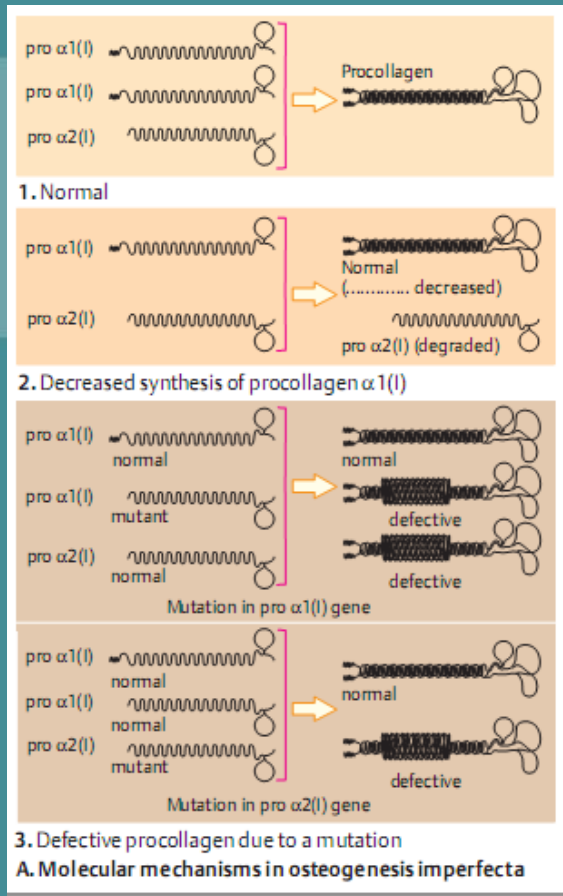
II. Chr.7

A group of inherited disorders of type1 collagen that predispose a patient to easy fracturing of bones, even with little trauma, and to skeletal deformity.

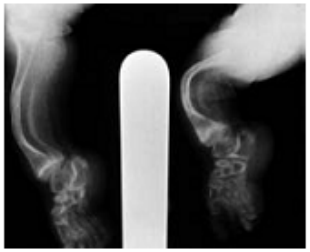


Osteogenesis Imperfecta





1. Bone deformation (OI type IV)



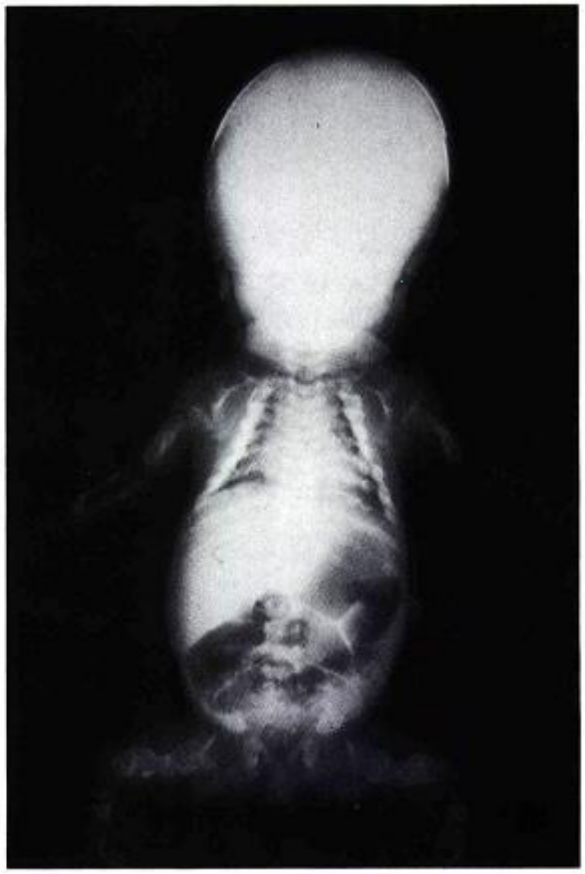
2. Severe deformation (OI type III)

3. Fatal form (OI type II)

C. Different forms of osteogenesis imperfecta

288

289



288 and 289 Osteogenesis imperfecta – congenital lethal type.

Note: Bowing of limbs, narrow deformed chest, beaked nose and high forehead.

X-rays: Note – gross shortening of long bones ('crumpled' appearance) with multiple fractures. The ribs are beaded due to multiple fractures *in utero*.

Other features: Wormian bones in the skull.

Inheritance: Some well-documented autosomal recessive sibships have been reported, but many cases are sporadic. A recurrence risk of 1 in 20 after a sporadic case is appropriate.

Compound Heterozygotes

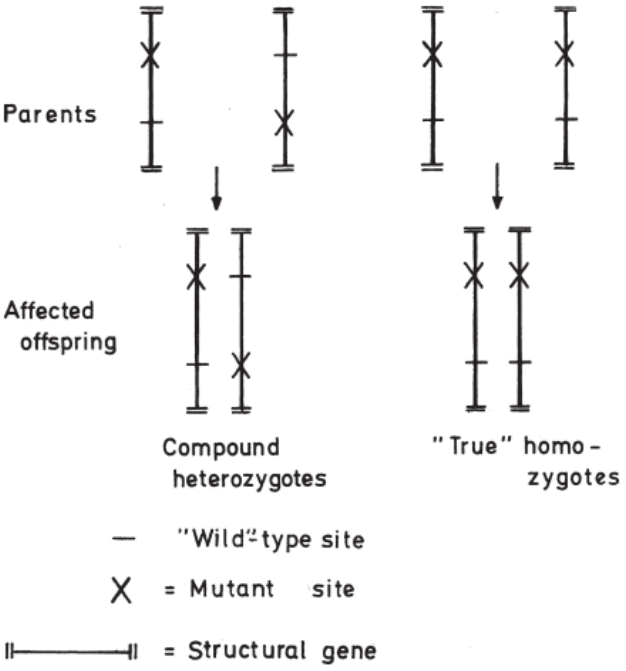
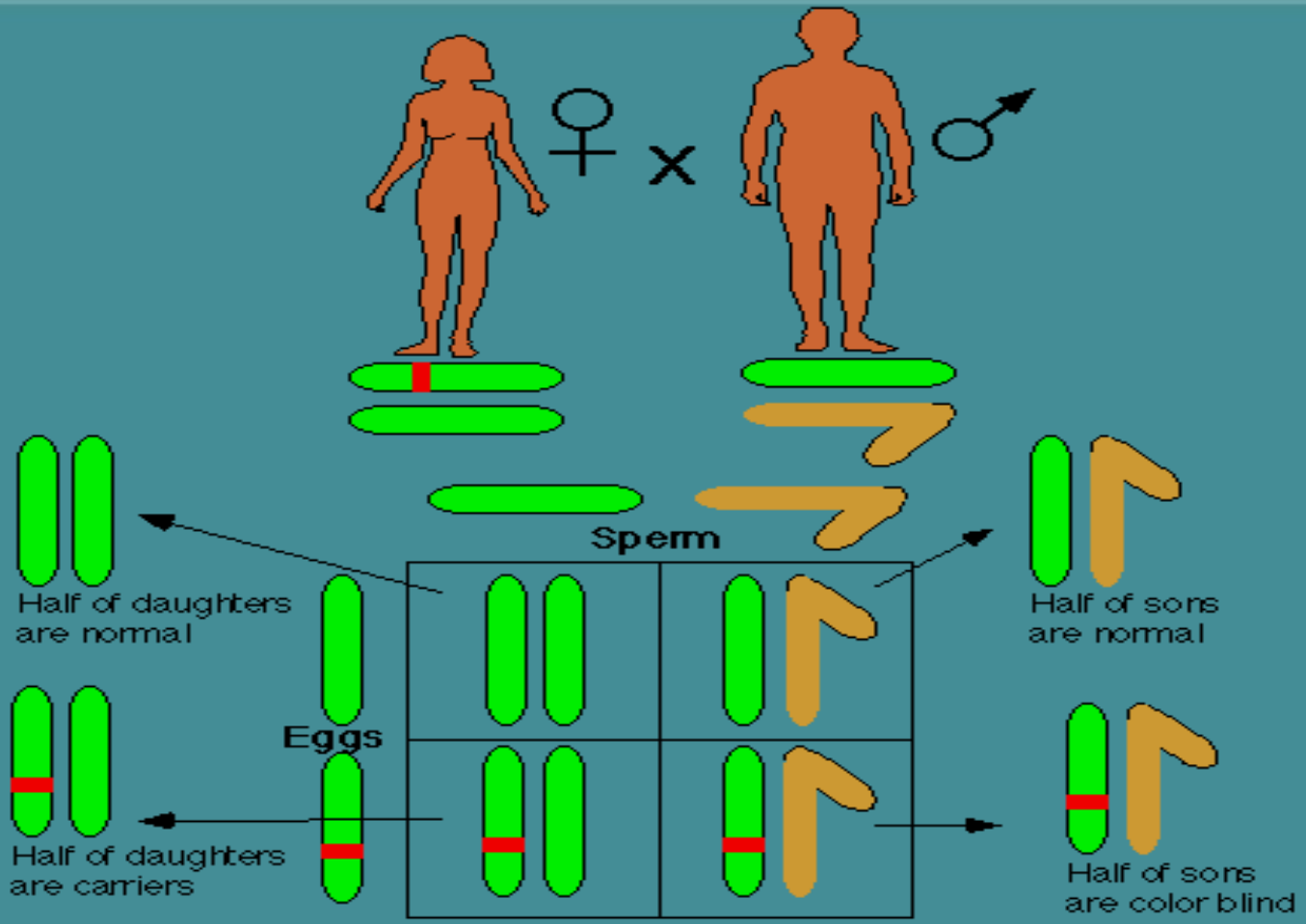


Fig. 5.10 Formation of a compound heterozygote. Each *line* represents the mutant locus on one chromosome in a parent. Among the many possibilities for mutation, two are shown. If parents are heterozygous for mutations that are at identical sites, the affected child is a "true" homozygote; otherwise, he or she is a compound heterozygote


♀ x ♂
Sperm
Eggs
Half of daughters are normal
Half of sons are normal
Half of daughters are carriers
Half of sons are color blind

X-Linked dominant (XD, XLD)

- a: Wt
- A: M

Male	Female
X^AY: Affected X^aY: Normal	X^AX^A: Affected (Homozygous) X^AX^a: Affected (Heterozygous) X^aX^a: Normal

- Frequency:

$$f(X^AX^A) + f(X^AX^a) = 2\, f(X^AY)$$

X-Linked dominant

X^AY (Affected) × X^aX^a (Normal)

↓

♂: X^aY (Normal) ; ♀: X^AX^a (Affected)

X^aY (Normal) × X^AX^a (Affected)

↓

♂: X^aY (Normal) : X^AY (Affected) ;

♀: X^AX^a (Affected) : X^aX^a (Normal)

♀ X^AX^a (Affected)

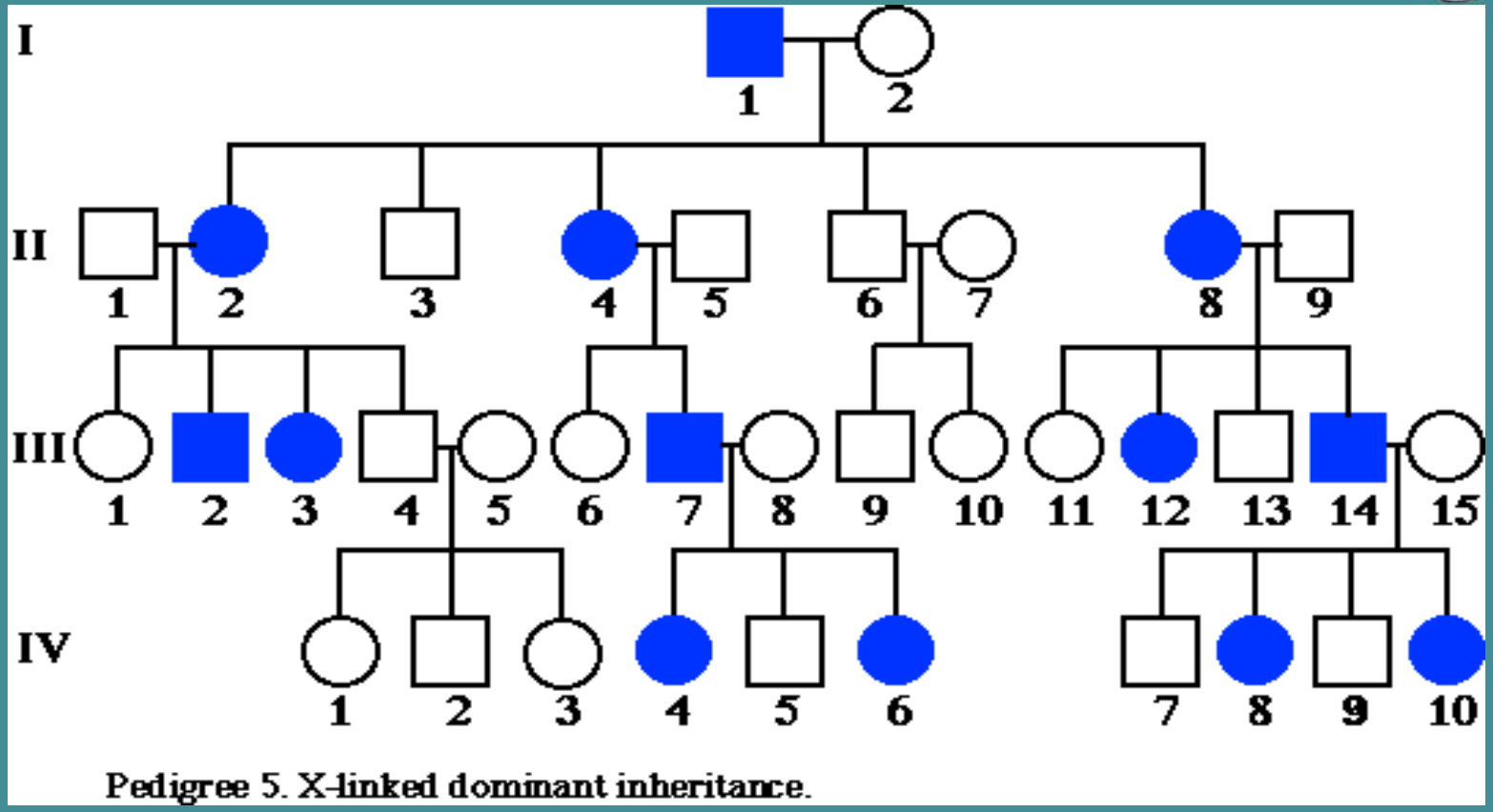
↑

Affected father or Affected mother

♂ X^AY (Affected)

↑

Affected mother



Pedigree 5. X-linked dominant inheritance.

X-Linked Dominant Inheritance with Lethality of the Male Hemizygotes

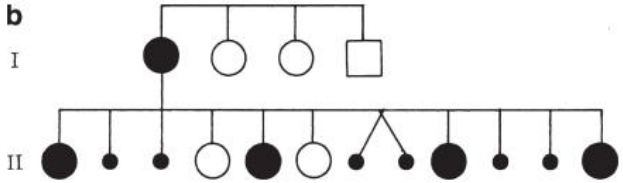
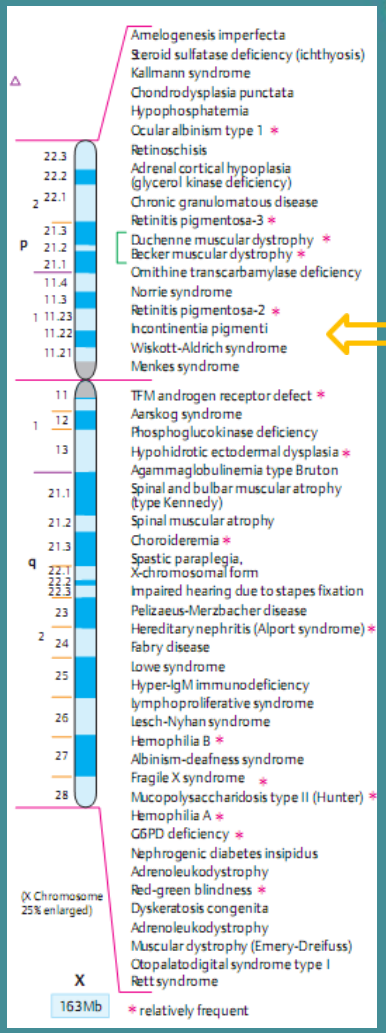


Fig. 5.14 (**a**) Incontinentia pigmenti (Bloch-Sulzberger; courtesy of Dr. W. Fuhrmann). Note the marble cake appearance of skin. (**b**) Pedigree of incontinentia pigmenti. •, Spontaneous abortion; ●, incontinentia pigmenti. From Lenz [47]

Incontinentia Pigmenti type 2 (IP2)

- Skin rash that begins in infancy
- Progress to thickening and hyperpigmentation
- Eventually, scarring and thinning
- Microcephaly
- Mental retardation
- Small or absent teeth
- Loss of hair

- Occures exclusively in females (is lethal in hemizygote males)



IP2

416

417

199

200

201

202

199–202 Oro-facio-digital syndrome type 1.
Note: Mid-line cleft of upper lip, cleft of hard and soft palate, multiple oral frenulae, shortening and syndactyly of toes and fingers.

Other features: Mental retardation, seizures, polydactyly and renal anomalies.

Inheritance: X-linked dominant. Hemizygous males probably die *in utero*.

328

329

328 and 329 Hypophosphataemic rickets.
X-ray: Note – metaphyseal widening with splayed, irregular and cupped appearance, rarefaction, coarse trabeculation and curvature of femora.

Other features: Curvature of long bones, 'pseudo-fractures', scoliosis, low serum phosphate, moderate elevation of alkaline phosphatase and hyperphosphaturia.

Inheritance: X-linked dominant.

X-Linked recessive (XR, XLR)

- A: Wt
- a: M

Male	Female
X^AY: Normal X^aY: Affected	X^AX^A: Normal X^AX^a: Normal (Carrier) X^aX^a: Affected

- Frequency:

$$f(X^AX^A) > f(X^AX^a)$$

$$f(X^aY) = \sqrt{f(X^aX^a)}$$

X-Linked recessive

X^AY (Normal) × X^aX^a (Affected)

↓

♀ : X^AX^a (Carrier) ; X^aY (Affected)

X^AY (Normal) × X^AX^a (Carrier)

↓

♀ : X^AX^A (Normal) : X^AX^a (Carrier) ;

♂ : X^AY (Normal) : X^aY (Affected)

X^aY (Affected) × X^AX^A (Normal)

↓

♀ : X^AX^a (Carrier) ; ♂ : X^AY (Normal)

X^aX^a

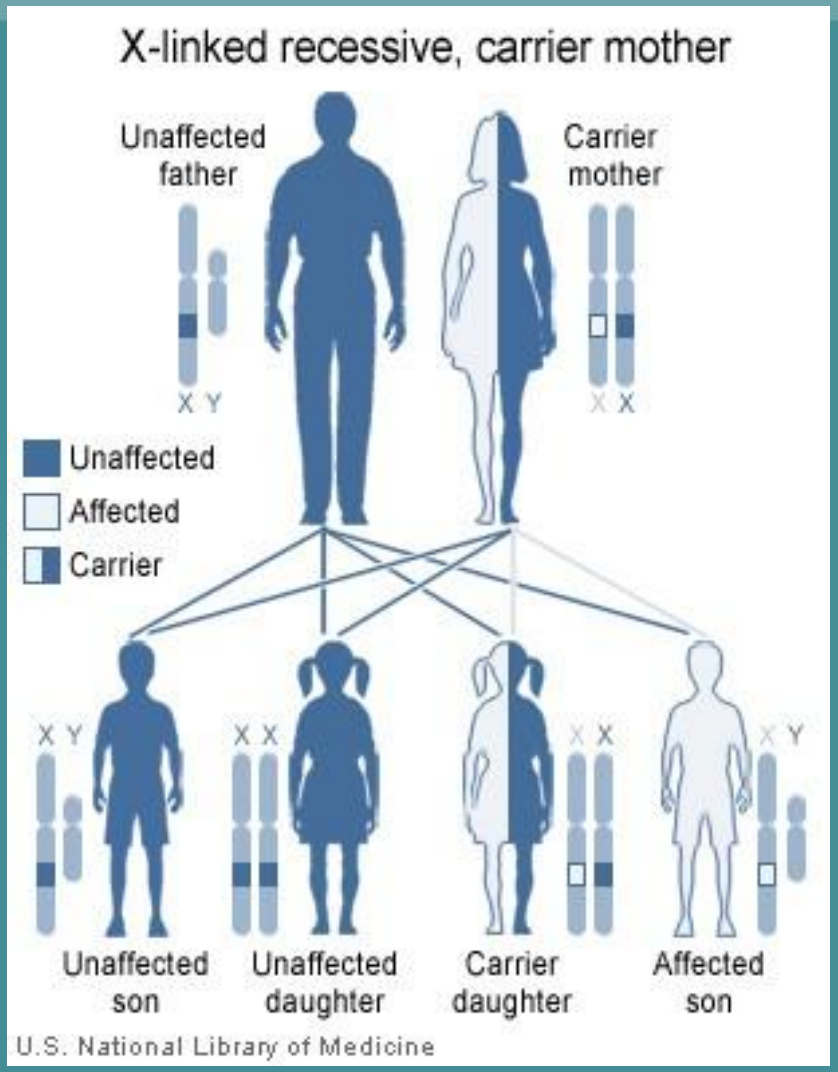
↑

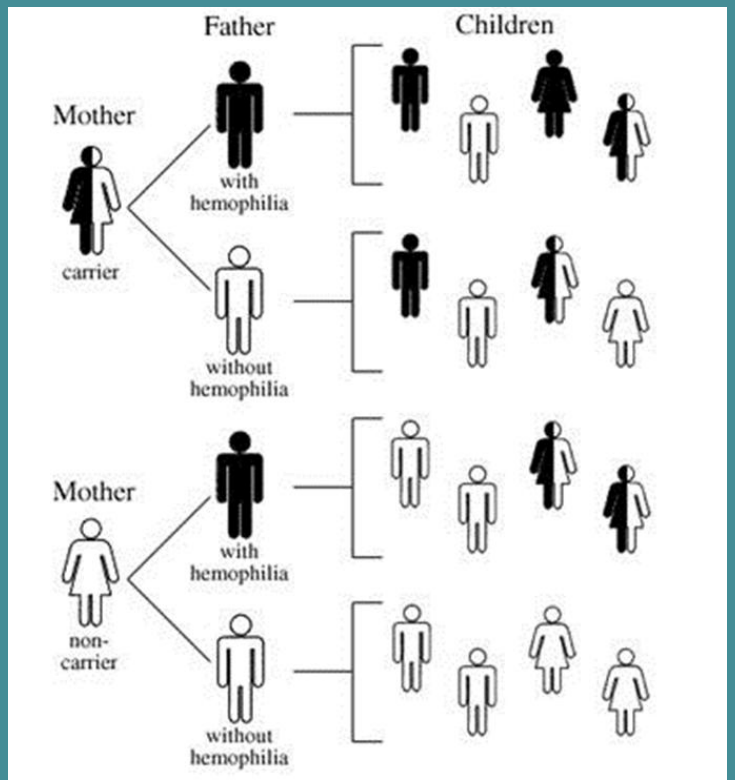
♂ X^aY (Affected)

X^aX^a

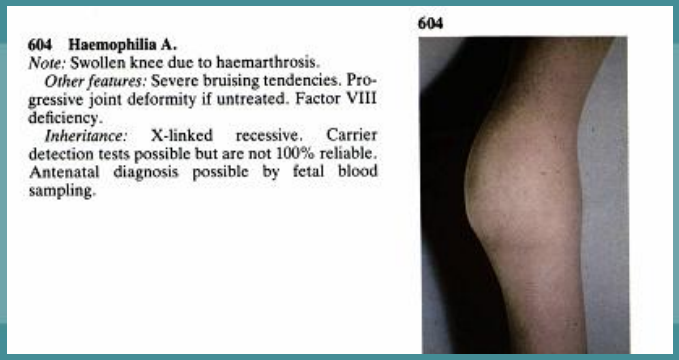
↓

X^aY (Affected)


X-linked recessive, carrier mother
Unaffected father
Carrier mother
X Y
X X
Unaffected
Affected
Carrier
X Y
X X
X X
X Y
Unaffected son
Unaffected daughter
Carrier daughter
Affected son
U.S. National Library of Medicine


Father
Children
Mother
carrier
with hemophilia
without hemophilia
Mother
non-carrier
with hemophilia
without hemophilia

Hemophilia A



604 Haemophilia A.
Note: Swollen knee due to haemarthrosis.
Other features: Severe bruising tendencies. Progressive joint deformity if untreated. Factor VIII deficiency.
Inheritance: X-linked recessive. Carrier detection tests possible but are not 100% reliable. Antenatal diagnosis possible by fetal blood sampling.

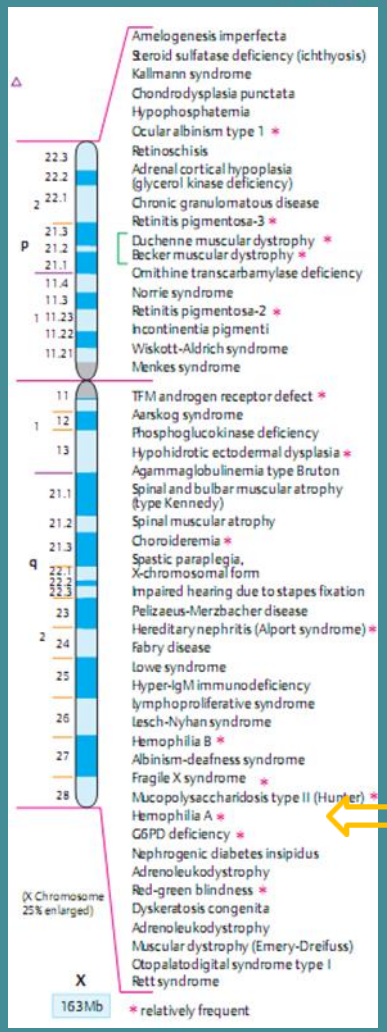
604

- Royal (classic) Hemophilia
- Deficiency of factor VIII :

<1% **Severe**

2-5% **Moderate**

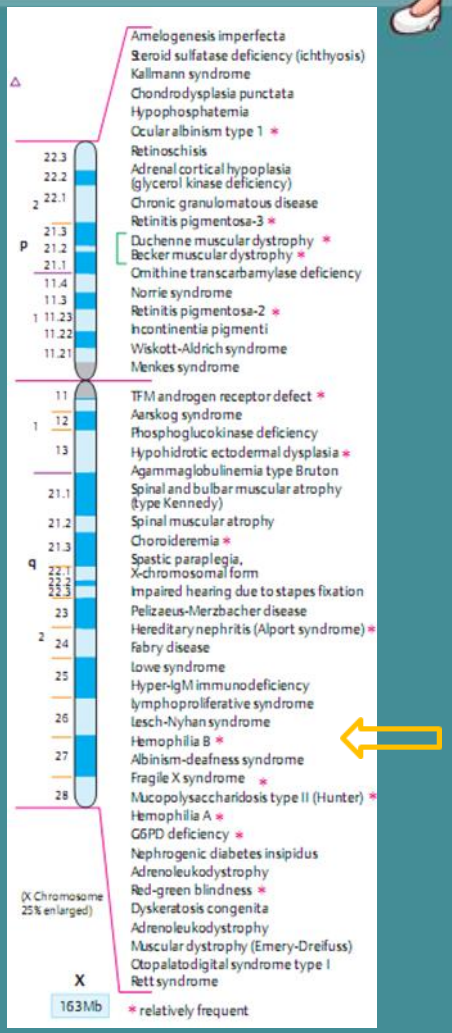
5-30% **Mild**



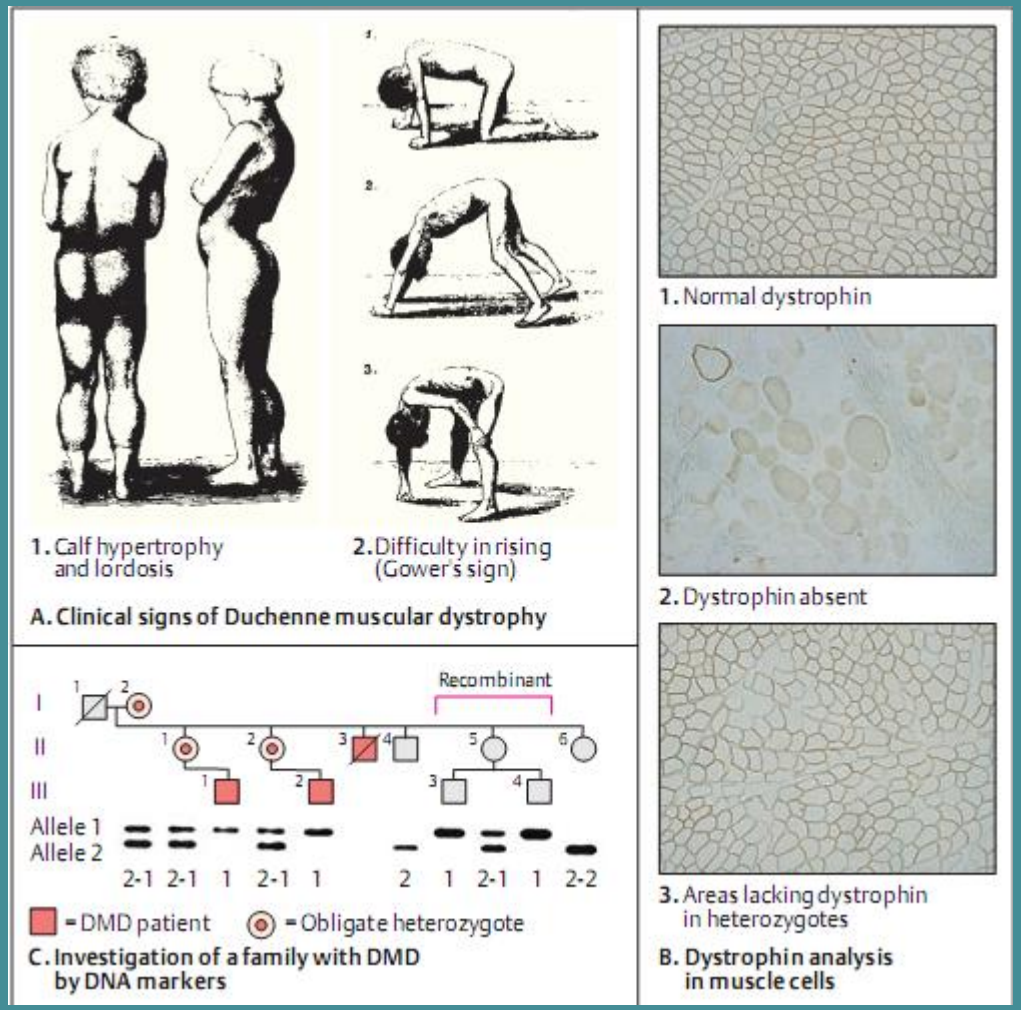
Hemophilia B
CHRISTMAS DISEASE

- Deficiency of factor IX

- Both are characterized by bleeding into soft tissues, muscles, and weight bearing joints.



Duchene Muscular Dystrophy (DMD)



DMD

483 Duchenne muscular dystrophy.
Note: Pseudohypertrophy of calves, proximal wasting in boy. Sister is a possible carrier.

Other features: Onset 2–3 years, mental retardation in some, scoliosis, cardiomyopathy, wheelchair bound by 11 years and death by end of 2nd decade.

Inheritance: X-linked recessive. One-third of all cases are thought to be new mutants. Measurement of serum creatine kinase in possible female heterozygotes may be used for carrier detection. Results of three separate tests should be combined statistically with pedigree data in order to arrive at a final probability.

483

484

484 Becker dystrophy.
Note: Pseudohypertrophy in a teenage boy who is still ambulent.

Other features: Proximal muscles of shoulder and pelvic girdle affected. Onset in 1st or 2nd decade, still ambulant at 11 years, generally not wheelchair bound before 3rd decade and occasional cardiomyopathy.

Inheritance: X-linked recessive.

547 Growth hormone deficiency.

Note: Severe short stature, mid-facial hypoplasia, prominent foreheads in offspring of consanguineous parents (these children are cousins from a highly inbred pedigree).

Inheritance: Most commonly autosomal recessive. X-linked recessive and autosomal dominant families have been described.

547

557

557 Testicular feminisation.
Note: Normal female habitus, scar in right groin where a testis was found in the inguinal canal.
Other features: 46, XY (male) karyotype, shortened vagina and absent uterus and end-organ unresponsiveness to testosterone.
Inheritance: X-linked recessive.

Antagonizers

- New mutation
- UPD (Uniparental disomy)
- LOH (Loss of heterozygosity)
- Non-Paternity
- Reduced penetrance
- X-inactivation (Manifesting heterozygote)

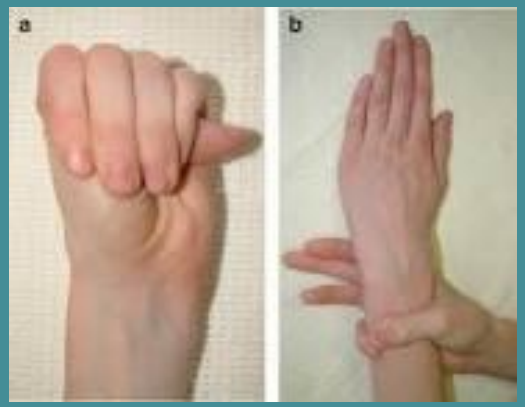
Reduced penetrance

- Penetrance in genetics is the proportion of individuals carrying a particular variant of a gene (allele or genotype) that also express an associated trait (phenotype). In medical genetics, the penetrance of a disease-causing mutation is the proportion of individuals with the mutation who exhibit clinical symptoms. For example, if a mutation in the gene responsible for a particular autosomal dominant disorder has 95% penetrance, then 95% of those with the mutation will develop the disease, while 5% will not.

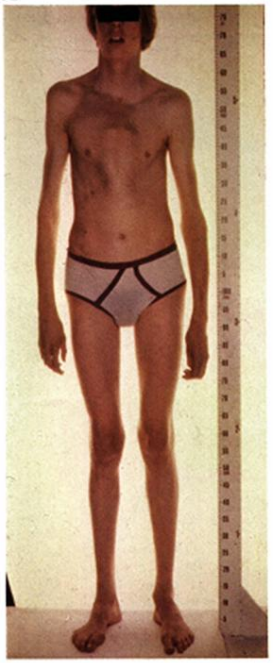
Variable expressivity

- Although some genetic disorders exhibit little variation, most have signs and symptoms that differ among affected individuals. Variable expressivity refers to the range of signs and symptoms that can occur in different people with the same genetic condition. For example, the features of Marfan syndrome vary widely— some people have only mild symptoms (such as being tall and thin with long, slender fingers), while others also experience life-threatening complications involving the heart and blood vessels. Although the features are highly variable, most people with this disorder have a mutation in the same gene (*FBN1*).

Marfan syndrome



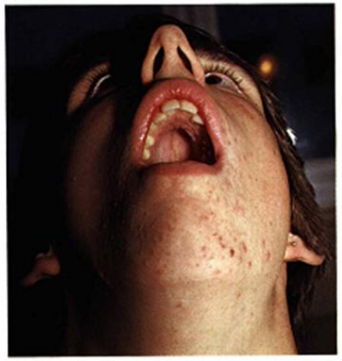
92



93

94

95



92–95 Marfan syndrome.
Note: Tall stature, reduced upper segment to lower segment ratio, pectus carinatum, long fingers and toes and high-arched palate.
Other features: Joint laxity, lens dislocation, dilatation of aortic root with regurgitation, floppy mitral valve and dissecting aneurysm.
Inheritance: Autosomal dominant.

Neurofibromatosis type I (NF1)

(Von-Recklinghausen disease)

- Growth of neurofibromas in skin
- Café-au-lait spots
- Lisch nodules
- Mental retardation
- CNS tumors
- Development of cancer of the nervous system or muscle

472

472–474 Neurofibromatosis (Von Recklinghausen).
Note:
(a) *Café au lait* spot and freckles in axilla.
(b) Multiple neurofibromata on limbs and trunk.
(c) Severe, multiple neuromata.
Other features: Pseudarthrosis of the tibia, scoliosis, neoplasms including meningiomas, gliomas, phaeochromocytomas, neurofibrosarcoma, acoustic neuromas, mental retardation (5–10%) and hypertension.
Inheritance: Autosomal dominant. Fifty per cent of cases are fresh mutants. High penetrance but variable expression.

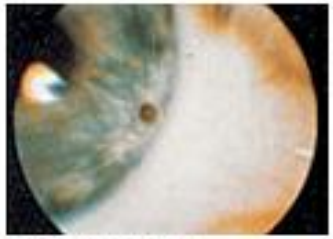
473

474

475

Neurofibromatosis 1 (NF1)
(von Recklinghausen disease)

- Autosomal dominant
- Frequency 1 in 3000
- Gene locus on 17q11.2
- Café-au-lait spots
- Lisch nodules in the iris
- Multiple neurofibromas
- Skeletal anomalies
- Predisposition to tumors of the nervous system
- 50% new mutations

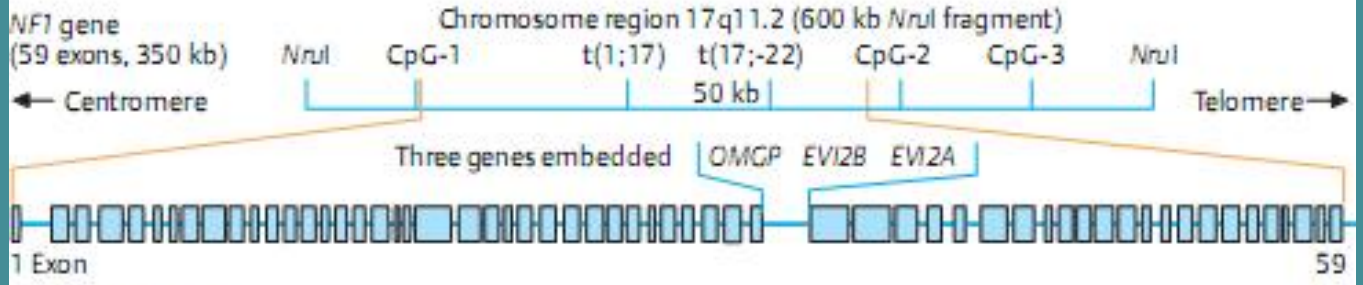


1. Lisch nodule

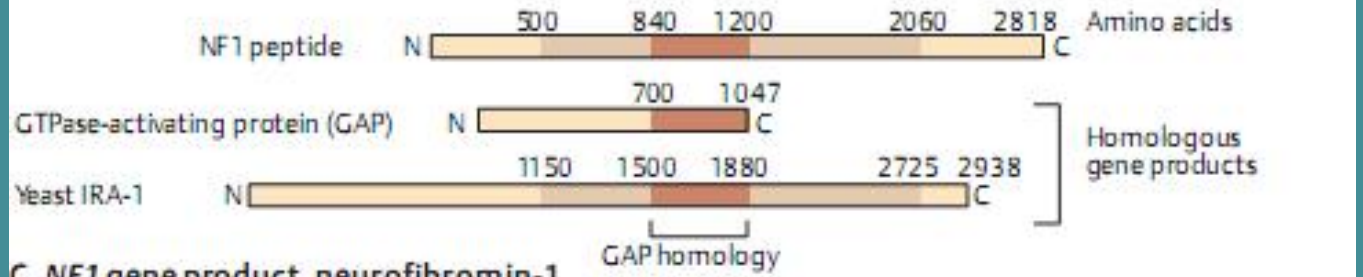
2. Café-au-lait spot

3. Neurofibromas

A. Main manifestations of neurofibromatosis 1



B. The *NF1* gene

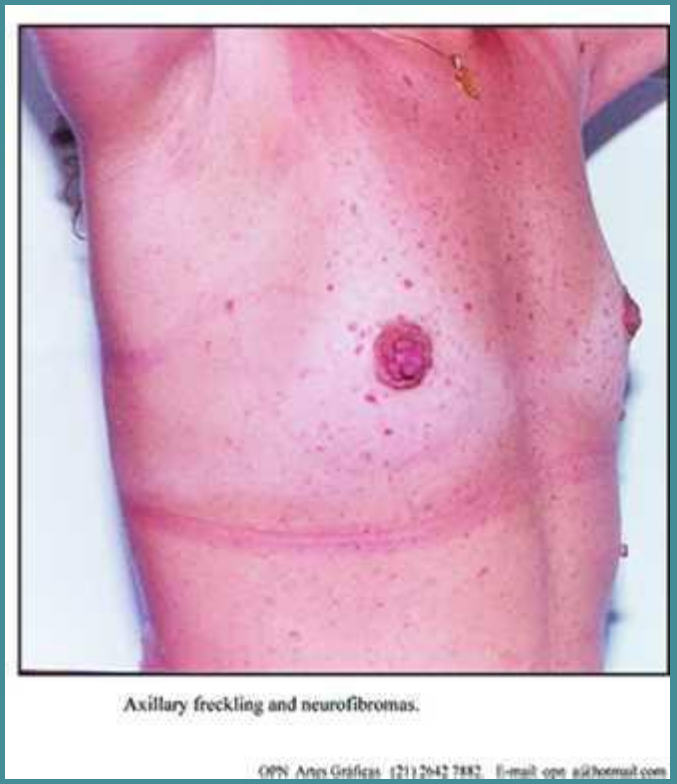


C. *NF1* gene product, neurofibromin-1

NF1

Café-au-Lait spot on the inferior lip mucosa

NF1



Axillary freckling and neurofibromas.

NF1

NF1

NF1

Causalty

1. **Environmemtal factors**

2. **Modifier genes:**

Epistasis is the phenomenon where the effects of one gene are modified by one or several other genes, which are sometimes called modifier genes. The gene whose phenotype is expressed is called epistatic, while the phenotype altered or suppressed is called hypostatic. Epistasis can be contrasted with dominance, which is an interaction between alleles at the same gene locus.

Modifying Genes in the AB0 Blood Group System

The best analyzed examples of modifying genes are offered by the AB0 blood group systems. Occurrence of the ABH antigens in saliva (and other secretions) depends on the secretor gene Se.

Homozygotes se/se are nonsecretors;

heterozygotes Se/se and homozygotes Se/Se are secretors.

Hence, se is a recessive suppressor gene.

Bhende et al. discovered a phenotype in 1952 which they called "**Bombay**". The erythrocytes were not agglutinated either by anti-A, anti-B or anti-H.

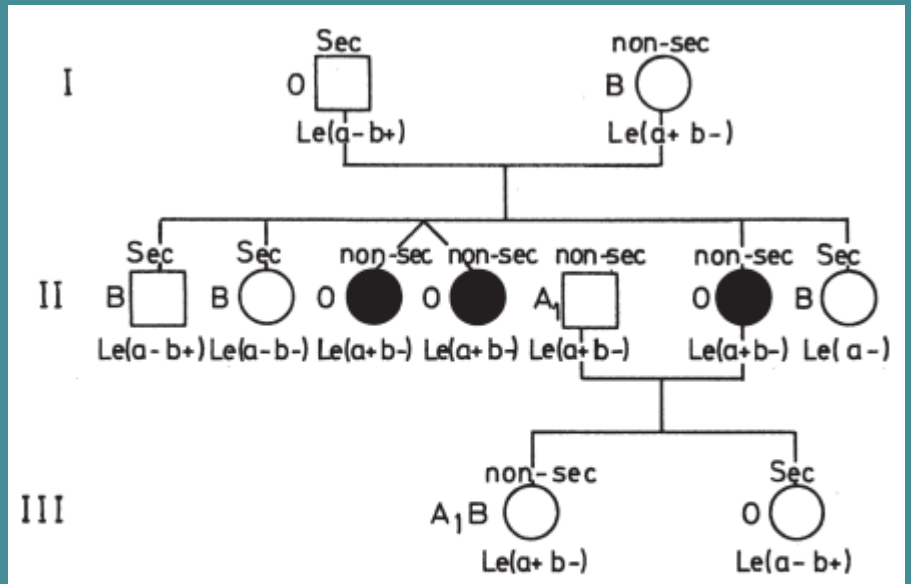
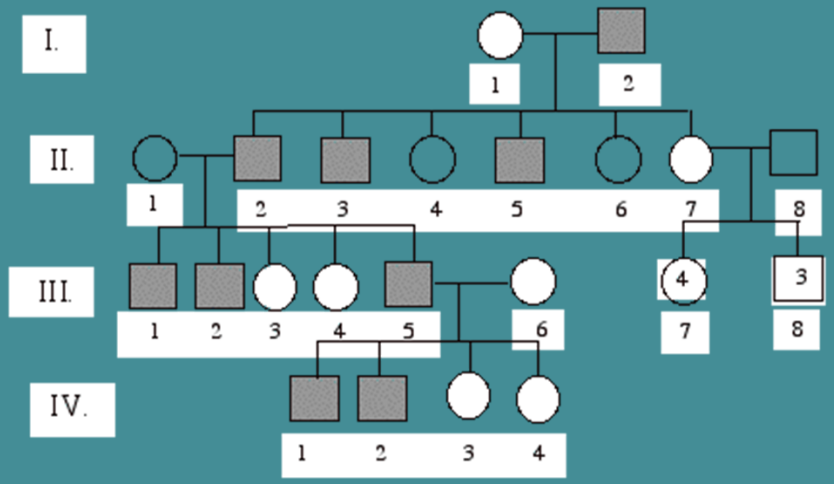


Fig. 5.15 The Bombay blood type. Manifestation of the B antigen is suppressed by a recessive gene x. Note that an O mother (II,6) has an A_1B child. From Bhende et al. [11]

Holandric inheritance

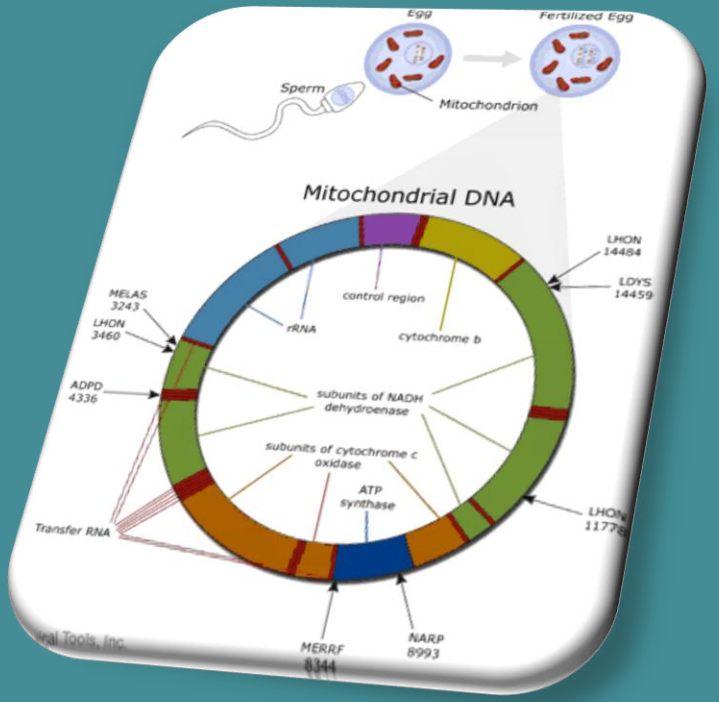
- Y-linked
- Male to male inheritance

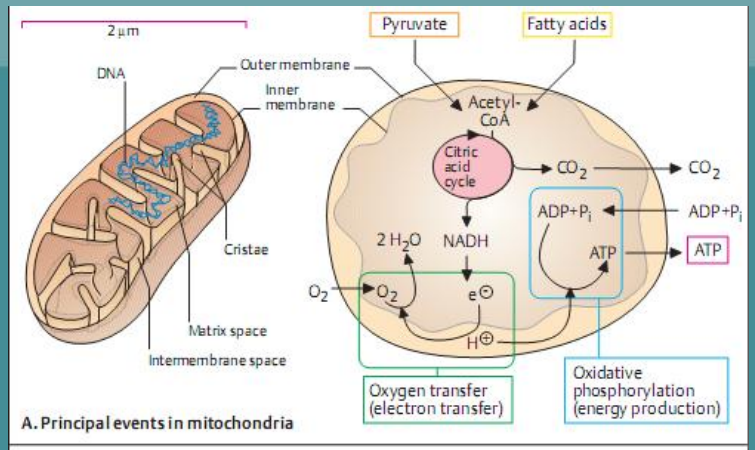


Holandric trait

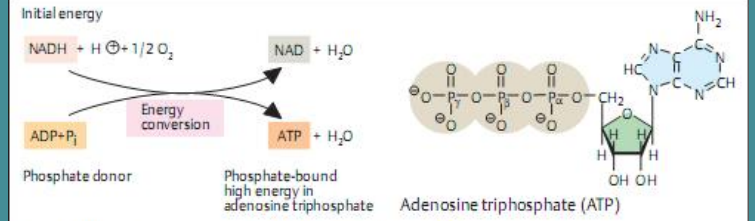
Mitochondrial inheritance

- Maternal inheritance
- Cytoplasmic inheritance

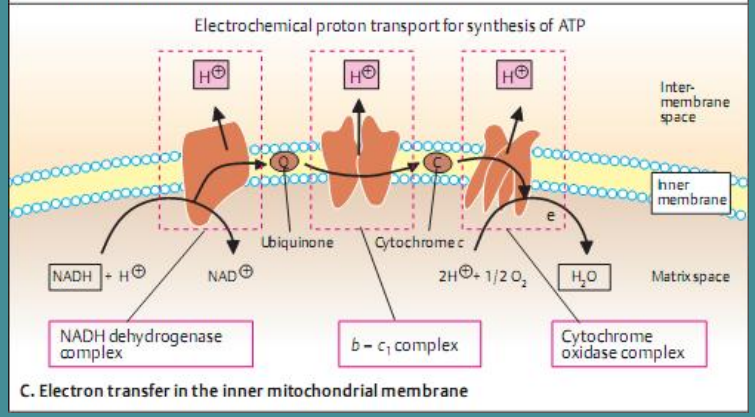




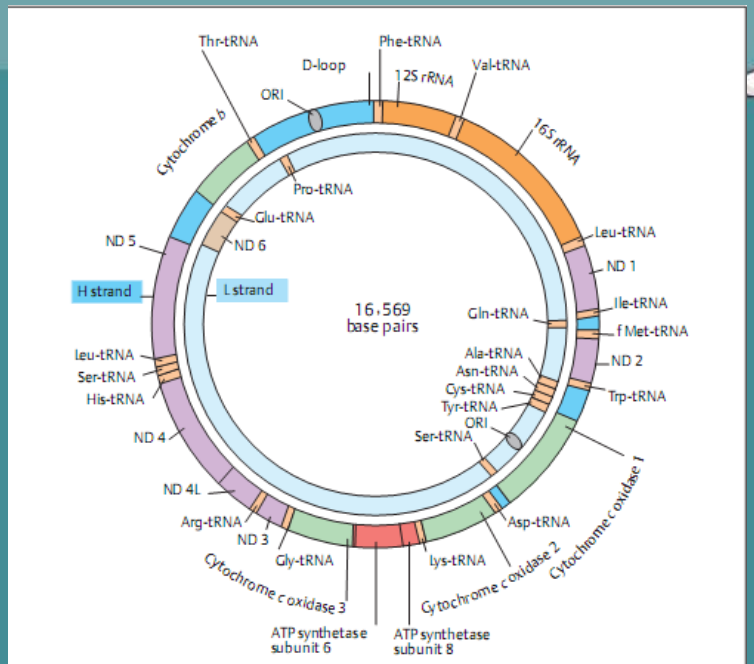
A. Principal events in mitochondria



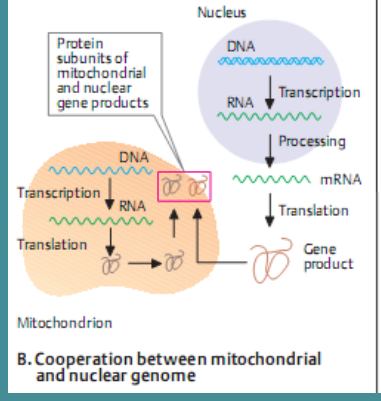
B. Oxidative phosphorylation (OXPHOS) in mitochondria



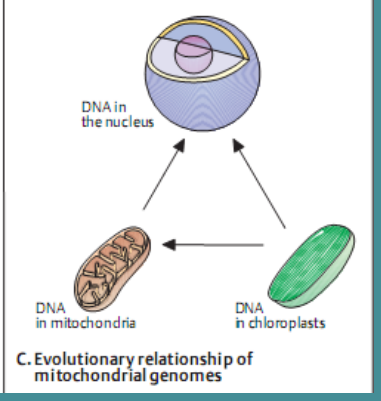
C. Electron transfer in the inner mitochondrial membrane



A. Mitochondrial genes in man



B. Cooperation between mitochondrial and nuclear genome

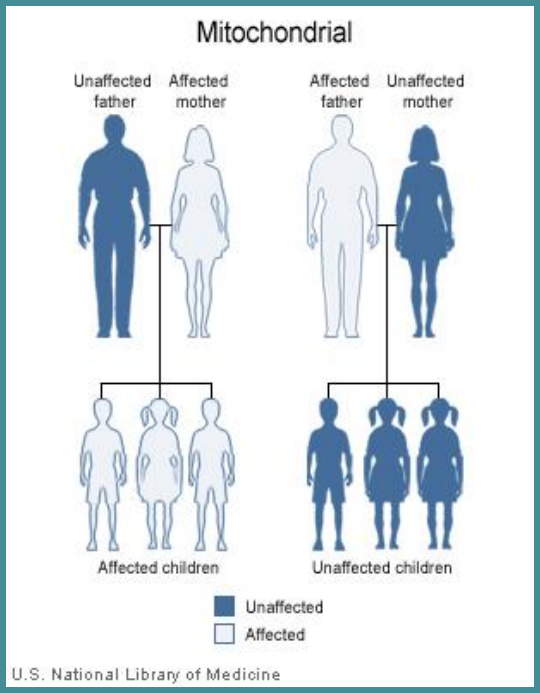


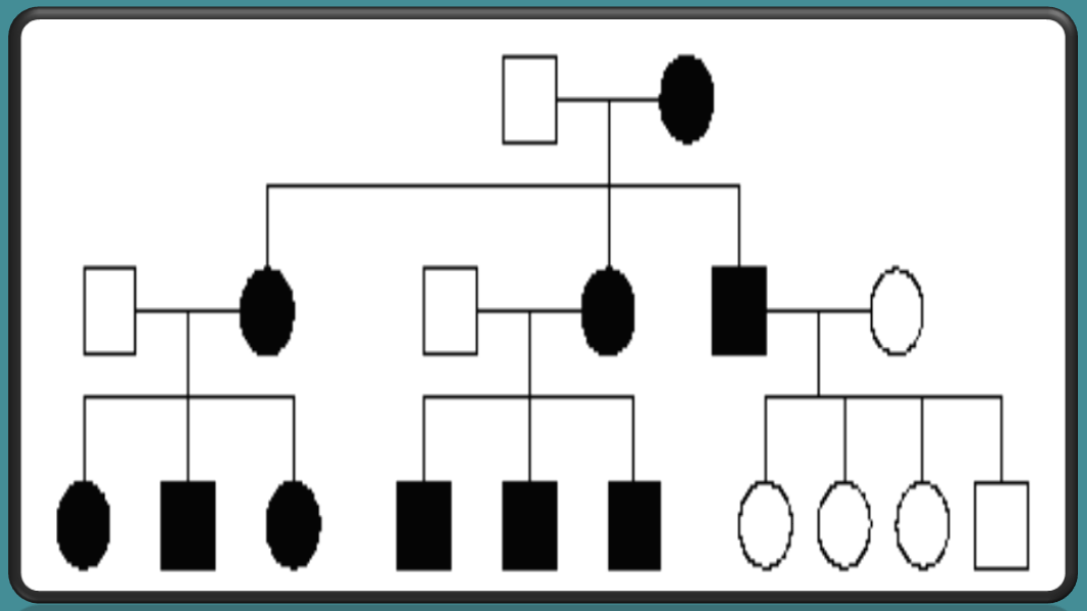
C. Evolutionary relationship of mitochondrial genomes

Differences between the universal genetic code and mitochondrial codes

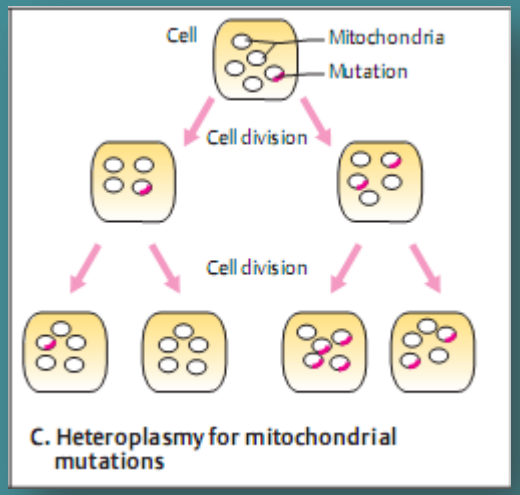
Codon	Universal code	Mitochondrial codes			
		Mammals	Invertebrates	Yeasts	Plants
UGA	Stop	Trp	Trp	Trp	Stop
AUA	Ile	Met	Met	Met	Ile
CUA	Leu	Leu	Leu	Thr	Leu
AGA/AGG	Arg	Stop	Ser	Arg	Arg

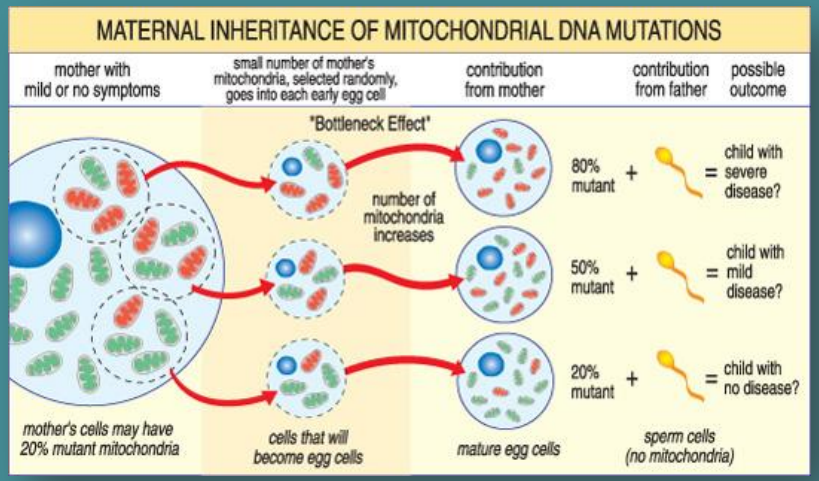
(Data from Alberts et al, 2002)


Mitochondrial
Unaffected father
Affected mother
Affected father
Unaffected mother
Affected children
Unaffected children
Unaffected
Affected
U.S. National Library of Medicine



- Homoplasm
- Heteroplasm





Examples of diseases due to mutations or deletions in human mitochondrial DNA[1]

MIM	Disease name	Abbreviation
530000	Kearns-Sayre syndrome (ophthalmoplegia, pigmentary retinal degeneration, cardiomyopathy)	KSS
535000	Leber hereditary optic atrophy	LHON
540000	Mitochondrial myopathy, encephalopathy, lactic acidosis	MELAS
545000	Myoclonus epilepsy with ragged red fibers in muscle	MERRF
551500	Neuropathy, ataxia, retinitis pigmentosa	NARP
603041	Mitochondrial neurogastrointestinal encephalopathy[2]	MNGIE
557000	Pearson marrow-pancreas syndrome	PEAR
515000	Chloramphenicol-induced toxicity	
580000	Deafness, aminoglycoside-induced (mutation A1555 G)	
520000	Diabetes-deafness syndrome, maternally transmitted	

1) Data from OMIM (www.ncbi.nlm.nih.gov/Omim).
2) This may be autosomal recessive.

- Sex-limited traits
- Sex-influenced traits

Table 5.3 Number of OMIM Entries, 25 May 2009

	Autosomal	X-Linked	Y-Linked	Mitochondrial	Total
* Gene with known sequence	12,111	581	48	37	12,777
+ Gene with known sequence phenotype	347	25	0	0	372
# Phenotype description, molecular basis known	2,293	207	2	26	2,528
% Mendelian phenotype or locus, molecular basis unknown	1,598	141	5	0	1,744
Other, mainly phenotypes with suspected Mendelian basis	1,900	139	2	0	2,041
Total	18,249	1,093	57	63	19,462

Uniparental disomy (UPD)

- In 1980 Eric Engel of the University of Geneva published a paper in which he discussed the possibility of having a chromosomal pair derived from only one parent. He termed this possibility “uniparental disomy” (UPD).

Mechanisms of UPD

- **Trisomy rescue**: the loss of a chromosome from an initial trisomy
- **Gamete complementation**: a mechanism by which a nullisomic gamete meets a disomy gamete. This mechanism implies two errors, one in each sex
- **Rescue of a monosomy**: the duplication of a singly inherited chromosome

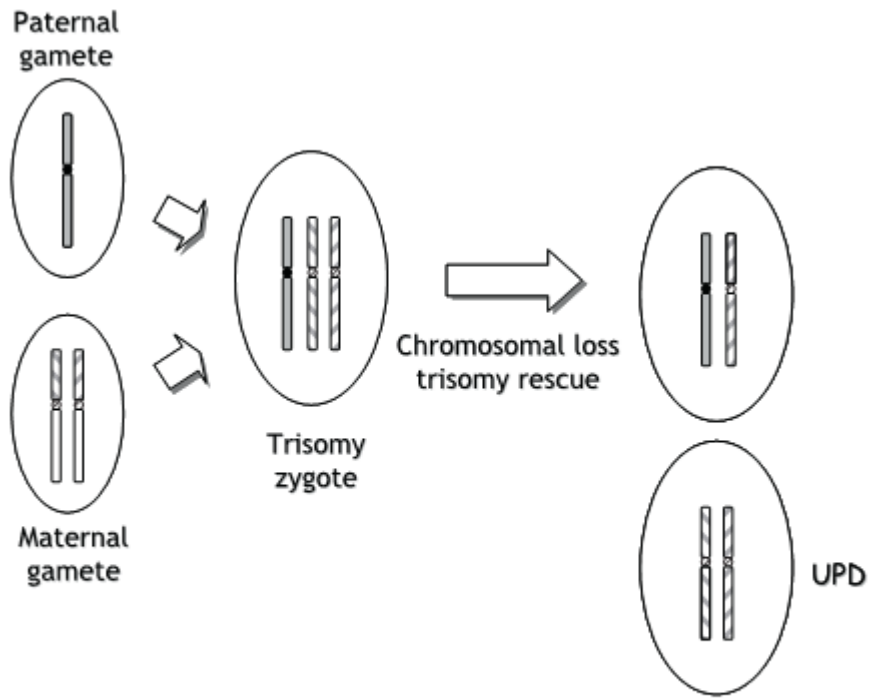


Fig. 5.18 Schematic representation of the mechanism of UPD due to trisomy rescue

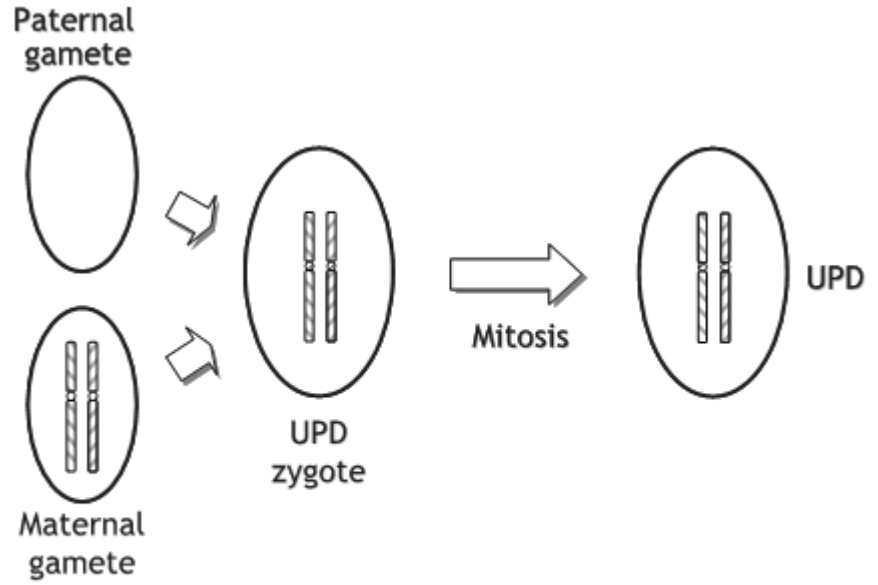


Fig. 5.19 Schematic representation of the mechanism of UPD due to gamete complementation

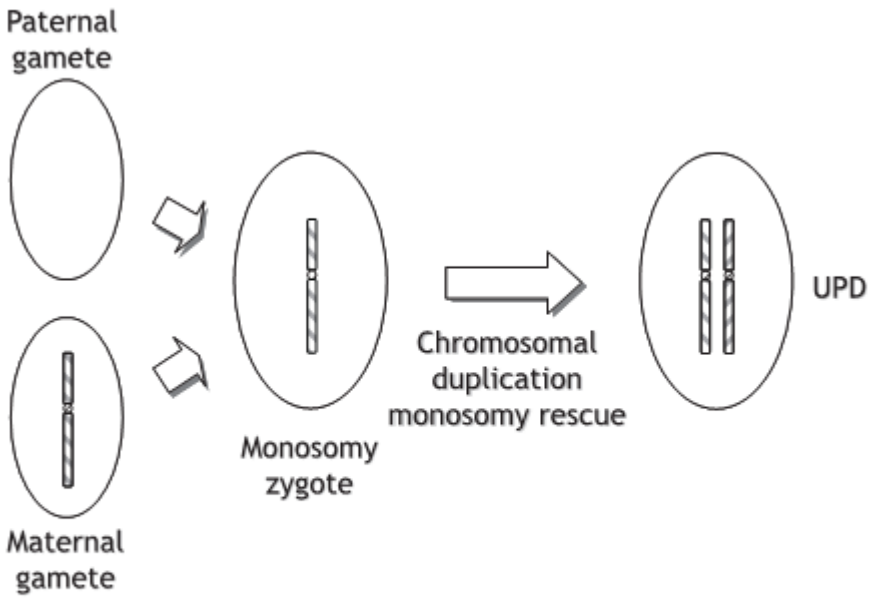


Fig. 5.20 Schematic representation of the mechanism of UPD due to monosomy rescue

Phenotypic Consequences of UPD

- **Duplication of autosomal recessive alleles**: In isodisomy, two copies of a mutant allele would result in the disease phenotype. In the originally described case of maternal UPD7, cystic fibrosis was due to two maternally derived copies of the Gly542Ter mutation of the CFTR genes (the mother in that case was a heterozygous carrier of this mutation).

- **Parental imprinting effects**

Human Disorders Involving UPD

- (a) Prader-Willi syndrome (matUPD15);
- (b) Angelmann syndrome (patUPD15);
- (c) Beckwith-Wiedemann syndrome (patUPD11p15);
- (d) neonatal transient diabetes mellitus in patUPD6;
- (e) maternal and paternal UPD14 syndromes;
- (f) some cases of Russell-Silver syndrome (matUPD7).

Genomic Imprinting

Prader-Willi Syndrome (PWS)

Angelman Syndrome (AS)

Prader Willi syndrome

- first described in 1956
- neonatal hypotonia
- facial dysmorphism
- poor feeding
- mild to moderate developmental delay
- hypogonadism in male
- excessive eating

Angelman (Happy puppet) syndrome

- first described in 1965
- mental retardation
- jerky, ataxic gait
- seizures
- absent speech
- excessive laughter /hand-flapping
- sleep disorders

197

198

197 and 198 Happy puppet syndrome (Angelman). *Note:* Deep-set eyes, prominent jaw, happy appearance and characteristic posture of arms.

Other features: Hypotonia, mental retardation, optic atrophy or choroidal dystrophy and seizures. Characteristic jerky movements are reminiscent of a string puppet.

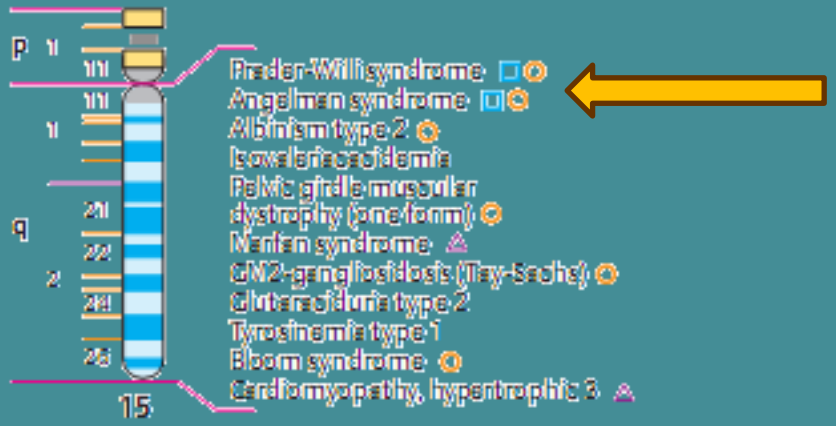
Inheritance: Most cases sporadic.

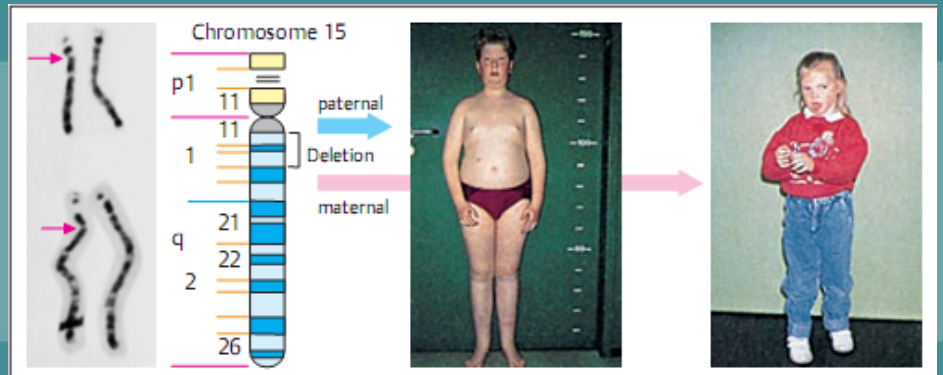
PWS vs AS

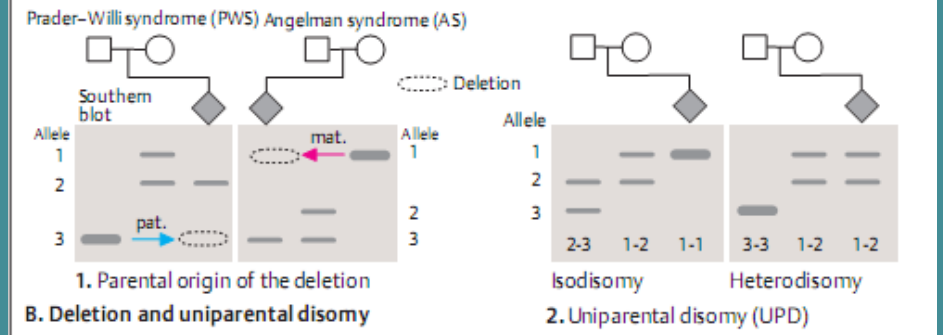
- **del 15 q11-13**

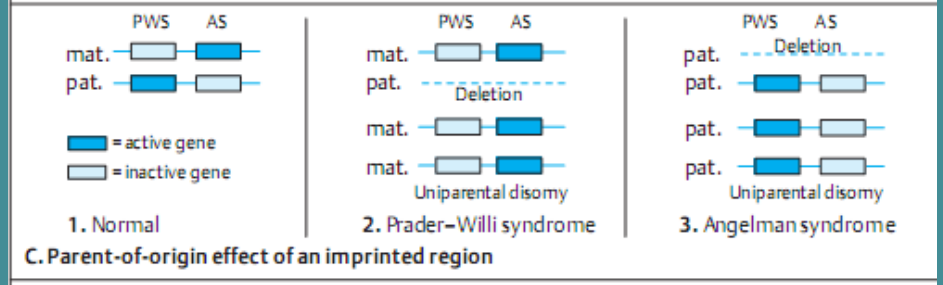
del 15 P ⟹ PWS

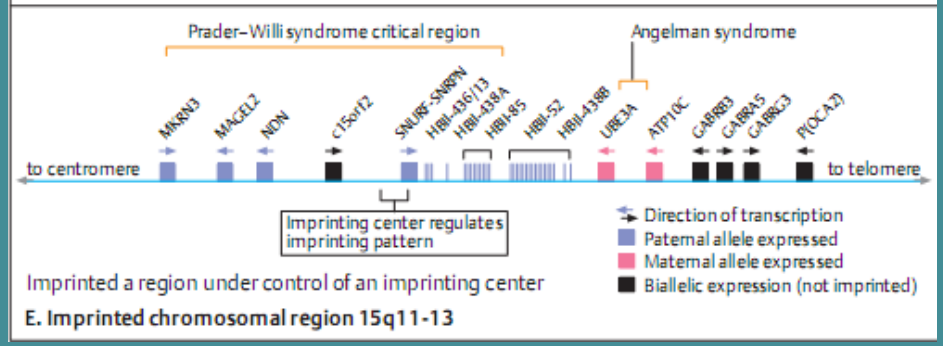
del 15 M ⟹ AS




Chromosome 15
p1
11
11
1
21
q
22
2
26
paternal
Deletion
maternal
1. Interstitial deletion 15q11-13
2. Prader–Willi syndrome
3. Angelman syndrome
A. Two syndromes associated with the same chromosomal region


Prader–Willi syndrome (PWS) Angelman syndrome (AS)
Southern blot
Allele
1
2
3
pat.
mat.
Deletion
Allele
1
2
3
Allele
1
2
3
2-3
1-2
1-1
3-3
1-2
1-2
1. Parental origin of the deletion
Isodisomy
Heterodisomy
2. Uniparental disomy (UPD)
B. Deletion and uniparental disomy

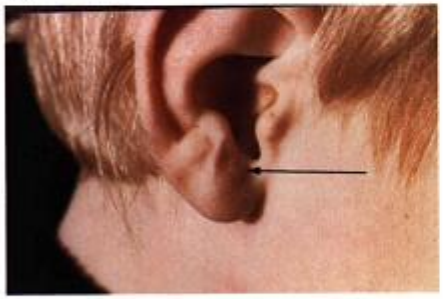

PWS
AS
mat.
pat.
= active gene
= inactive gene
1. Normal
PWS
AS
mat.
pat.
Deletion
mat.
mat.
Uniparental disomy
2. Prader–Willi syndrome
PWS
AS
Deletion
pat.
pat.
pat.
pat.
Uniparental disomy
3. Angelman syndrome
C. Parent-of-origin effect of an imprinted region


Prader–Willi syndrome critical region
Angelman syndrome
MKRN3
MAGEL2
NDN
c15orf2
SNURF-SNRPN
HBII-436/13
HBII-438A
HBII-85
HBII-52
HBII-438B
UBE3A
ATP10C
GABRB3
GABRA5
GABRG3
P(OCA2)
to centromere
to telomere
Imprinting center regulates imprinting pattern
Direction of transcription
Paternal allele expressed
Maternal allele expressed
Biallelic expression (not imprinted)
Imprinted a region under control of an imprinting center
E. Imprinted chromosomal region 15q11-13

240

241

242



243

240–243 Beckwith–Wiedemann syndrome.
Note: Large tongue with open mouth. Infra-orbital hypoplasia. Horizontal creases on the lobe (arrow) of the ear together with small, punched-out pits behind the helix (arrow).

Other features: Accelerated growth and osseous maturation, omphalocele, organomegaly, diaphragmatic eventration, pancreatic islet cell hyperplasia leading to hypoglycaemia.

Inheritance: Mostly sporadic, but occasional dominant pedigrees described.